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No. 86-

IN THE

Supreme Court of the United States

OCTOBER TERM, 1986

NORWICH EATON PHARMACEUTICALS, INC.,
Petitioner,

v.

OTIS R. BOWEN, Secretary of Health and Human Services; FRANK E. YOUNG, M.D., Ph.D., Commissioner of Food and Drugs; UNITED STATES FOOD AND DRUG ADMINISTRATION,
Respondents.

PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

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QUESTIONS PRESENTED FOR REVIEW

1. In reversing the decision of the District Court in a case involving application of the non-patent exclusivity provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 ("the 1984 Amendments"), did the Court of Appeals improperly defer to the legal and factual conclusions of the Food and Drug Administration where 1) the agency had not followed proper procedures in considering the matter; 2) the matter was not within the expertise of the agency; and 3) the agency was not in a position to consider the matter on an impartial basis?

2. Does the decision of the Court of Appeals, concurring with FDA's determination that Petitioner's new drug product Buprenex (buprenorphine hydrochloride) Injection was "approved" on December 29, 1981 and is therefore not entitled to any non- patent exclusivity, conflict with the provisions of the 1984 Amendments and defeat the express intent of Congress in enacting those provisions?

PARTIES

In addition to those parties listed in the caption, Petitioner notes in accordance with Rule 28.1 that it is a wholly-owned subsidiary of the Procter & Gamble Co., and that Norwich Overseas (a wholly-owned subsidiary of Norwich Eaton) owns a 50% interest in Rohm Pharma, GmbH, with the remaining 50% interest owned by Rohm GmbH.

TABLE OF CONTENTS

	Page
QUESTIONS PRESENTED FOR REVIEW	i
PARTIES	ii
TABLE OF CONTENTS	iii
TABLE OF AUTHORITIES	v
OPINIONS BELOW	1
JURISDICTION	2
STATUTES INVOLVED	2
STATEMENT OF THE CASE	2
I. Introduction: The Drug Product Buprenex...	3
II. Statutory Background	4
A. The Approval Requirements of the FFDCA	4
B. The Interrelationship Between the FFDCA and the Status of a Drug Under the Controlled Substances Act	5
III. The Approval of Buprenex	6
IV. Statutory Changes Affecting The Status of Buprenex	11
V. The Proceedings Below	13
REASONS FOR GRANTING THE WRIT	15
I. Introduction—The Precedential Significance of This Case	15
II. The Court of Appeals Improperly Concluded That FDA's Definition of "Approval" is Consistent With The Statutory and Regulatory Standards	18
III. The Court of Appeals Applied An Improperly Deferential Standard of Review to FDA's Position in This Case	22

A. Failure to Follow Essential Procedural Safeguards 23
B. Lack of Applicable Agency Expertise ... 24
C. Bias Inherent in the Agency's Decision 27

CONCLUSION 29

Appendices

Appendix A—*Norwich Eaton Pharmaceuticals, Inc. v. Bowen, et al.*, 808 F.2d 486 (6th Cir. 1987) 1a

Appendix B—*Norwich Eaton Pharmaceuticals, Inc. v. Bowen, et al.*, 645 F. Supp. 321 (S.D. Ohio 1986) 15a

Appendix C—Letter from FDA Center For Drugs and Biologics denying Norwich's Citizen Petition (December 4, 1985) 22a

Appendix D—Provisions of 21 C.F.R. §§201 and 314, (1981) and (1986), cited in pertinent part 31a

Appendix E—21 U.S.C.A. §355 (West Supp. 1986), cited in pertinent part 36a

TABLE OF AUTHORITIES

CASES: Page

Camp v. *Pitts*, 441 U.S. 138 (1973) 23

Carson Products Co. v. *Califano*, 594 F.2d 453 (5th Cir. 1979) 24

Citizens to Preserve Overton Park v. *Volpe*, 401 U.S. 402 (1971) 23

Del Laboratories, Inc. v. *United States*, 86 F.R.D. 676 (D.D.C. 1980) 24

Federal Maritime Comm. v. *Seatrain*, 411 U.S. 726 (1973) 25

FTC v. *Motion Picture Advertising Service Co.*, 344 U.S. 392 (1953) 25

Genstar Chemical Ltd. v. *ICC*, 491 F. Supp. 391 (D.D.C. 1980), rev'd on other grounds, 665 F.2d 1304 (D.C. Cir. 1981), *cert. denied*, 456 U.S. 905 (1982) 25

In re Murchison, 349 U.S. 133 (1955) 28

Jicarilla Apache Tribe v. *Fed. Energy Reg. Comm.*, 578 F.2d 289 (10th Cir. 1978) 25

Mead Johnson Pharmaceutical Group v. *Bowen, Civ. No.* 85-3971 (D.D.C. January 27, 1987) 17

Miller v. *City of Mission, Kansas*, 705 F.2d 368 (10th Cir. 1983) 28

Montgomery Imp. Ass'n. Inc. v. *U.S. Dept. of HUD*, 543 F. Supp. 603 (M.D. Ala. 1982), aff'd, 645 F.2d 291 (5th Cir. 1981) 24

Morton v. *Ruiz*, 415 U.S. 199 (1974) 26

NLRB v. *Brown*, 380 U.S. 278 (1965) 26

Norwich Eaton Pharmaceuticals, Inc. v. *Bowen*, 645 F. Supp. 321 (S.D. Ohio 1986) ..... *passim*

Norwich Eaton Pharmaceuticals, Inc. v. *Bowen*, 808 F.2d 486 (6th Cir. 1987) ..... *passim*

NOW, Washington, D.C. Chapter v. *Social Security Administration*, 736 F.2d 727 (D.C. Cir. 1984) 24

Table of Authorities Continued

	Page
Pickering v. *Board of Education*, 391 U.S. 563 (1968)	29
Porter v. *Califano*, 592 F.2d 770 (5th Cir. 1979)	29
SEC v. *Sloan*, 436 U.S. 103 (1978)	26
Skidmore v. *Swift and Co.*, 323 U.S. 134 (1944)	27
Volkswagonwerk v. *Federal Maritime Comm.*, 390 U.S. 261, modified on other grounds, 392 U.S. 901 (1968)	26
Withrow v. *Larkin*, 421 U.S. 35 (1975)	28
Zotos International, Inc. v. *Kennedy*, 460 F. Supp. 268 (D.D.C. 1978)	24
STATUTES AND REGULATIONS:	
Controlled Substances Act, 21 U.S.C. § 801 *et seq.*	*passim*
Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, codified in part at 21 U.S.C. §355	*passim*
Federal Food, Drug and Cosmetic Act, 21 U.S.C. §301 *et seq.*	*passim*
Freedom of Information Act, 5 U.S.C. §552	11
5 U.S.C. §706	14
21 U.S.C. §321(p)	4
21 U.S.C. §355	2,7
21 U.S.C. §355(a)	4
21 U.S.C. §355(b)	11
21 U.S.C. §355(c)(1)	4
21 U.S.C. §355(d)	4
21 U.S.C. §355(j)	12
21 U.S.C. §355(j)(2)(A)	12

Table of Authorities Continued

	Page
21 U.S.C. §355(j)(4)(D)	*passim*
21 U.S.C. §355(j)(6)(A)(i)(I)	19
21 U.S.C. §811(b)	5
21 U.S.C. §812(b)	3,8
21 U.S.C. §812(c)	3
28 U.S.C. §2101(c)	2
28 U.S.C. §1254(1)	2
28 U.S.C. §1331 *et seq.*	14
35 U.S.C. §156	16
21 C.F.R. §10.3(a)	23
21 C.F.R. §10.30(j)	24
21 C.F.R. §10.65(d)(3)	23
21 C.F.R. §10.65(f)(2)	23
21 C.F.R. §201.56	4
21 C.F.R. §201.57	4,18
21 C.F.R. §201.57(h)	5
21 C.F.R. §201.57(h)(1)	15,18,20
21 C.F.R. §310.300(b)(4)(i) (1981)	10
21 C.F.R. §314.1(c)(2) (1981)	22
21 C.F.R. §314.10 (1981)	20,22
21 C.F.R. §314.14 (1981)	11
21 C.F.R. §314.50	4
21 C.F.R. §314.50(d)(5)(vii)	6
21 C.F.R. §314.50(e)(2)(ii)	4
21 C.F.R. §314.80(c)(2)	10
21 C.F.R. §314.100(d) (1981)	22
21 C.F.R. §314.105	4,18
21 C.F.R. §314.110	5,21
21 C.F.R. §314.120	4

Table of Authorities Continued

	Page
21 C.F.R. §314.125(b)	4
21 C.F.R. §314.430	11
21 C.F.R. §1302.03(c)	8
LEGISLATIVE MATERIALS	
Cong. Rec. S10,503 (Aug. 10, 1984)	12
Cong. Rec. H9,113 (Sept. 6, 1984)	26
H. Rep. 98-857, 98th Cong., 2d Sess., *reprinted in* 1984 U.S. Code Cong. & Ad. News 2,647	11,26
OTHER:	
39 Fed. Reg. 44602 (December 24, 1974)	12
47 Fed. Reg. 46621 (October 19, 1982)	5,22
50 Fed. Reg. 8104 (February 28, 1985)	3,10
51 Fed. Reg. 10190 (March 25, 1986)	6
51 Fed. Reg. 22085 (June 18, 1986)	16
51 Fed. Reg. 25338 (July 11, 1986)	27
51 Fed. Reg. 26341 (July 22, 1986)	5
52 Fed. Reg. 6221 (March 2, 1987)	17
52 Fed. Reg. 7035 (March 6, 1987)	16
52 Fed. Reg. 7214 (March 9, 1987)	17
Approved Prescription Drug Product List, 5th ed. (July 1984)	19
Speech by James C. Morrison, Deputy Director, FDA Office of Drug Standards, at Food & Drug Law Institute, Washington, D.C. (December 9, 1986)	25
FDC Reports 44:2 (January 11, 1982)	28

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PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

OPINIONS BELOW

This petition seeks review of a January 9, 1987 decision of the United States Court of Appeals for the Sixth Circuit, reported as *Norwich Eaton Pharmaceuticals, Inc. v. Bowen*, No. 86-3397, 808 F.2d 486 (6th Cir. 1987). This decision is reproduced as Appendix A.

Petitioner's suit was originally the subject of a "Citizen Petition" to the Food and Drug Administration, which was rejected on December 4, 1985. (*See* Appendix C.) Subsequent to the FDA decision, Petitioner sought a declaration of its rights from the United States District Court for the Southern District of Ohio, which held in favor of Petitioner.

Norwich Eaton Pharmaceuticals, Inc. v. Bowen, Civil No. C-1-85-1914, 645 F. Supp. 321 (S.D. Ohio 1986), reproduced as Appendix B.

JURISDICTION

The decision of the Court of Appeals was entered on January 9, 1987. This petition was filed within 90 days of the date of the Court of Appeals judgment as per 28 U.S.C. §2101(c). This Court's jurisdiction is invoked under 28 U.S.C. §1254(1).

No Petition for Rehearing was filed.

STATUTES INVOLVED

Because of the length of the statute involved herein, 21 U.S.C. §355, and regulations promulgated thereunder at 21 C.F.R. §§201 and 314, the relevant portions of the statute and regulations are set out at Appendices D and E.

STATEMENT OF THE CASE

Petitioner, Norwich Eaton Pharmaceuticals, Inc. ("Norwich"), Plaintiff-Appellee below, is the holder of an approved new drug application ("NDA") for the drug product Buprenex Injection. On December 27, 1985, Norwich brought a declaratory judgment action to enforce its exclusivity rights with respect to Buprenex as conferred by the Drug Price Competition and Patent Term Restoration Act of 1984. These rights preclude FDA from granting effective approval of an abbreviated new drug application for a copy of the drug until the exclusivity expires.[1] On March 3, 1986, the District Court issued an order determining that Norwich was entitled to five years of exclu-

[1] The exclusivity provisions at issue do not preclude effective approval of a copy of Buprenex pursuant to a full NDA containing reports of clinical investigations generated by or for the second applicant.

sivity for Buprenex beginning June 28, 1985. (Appendix B.) This ruling was reversed on January 9, 1987 by the Court of Appeals for the Sixth Circuit. (Appendix A.) Petitioner seeks a writ of certiorari to the Sixth Circuit and review by this Court of the January 9, 1987 decision.

I. Introduction: The Drug Product Buprenex

The active drug ingredient in Buprenex Injection is buprenorphine hydrochloride, an extremely potent new analgesic drug that is used in the treatment of moderate to severe pain. Because of its unique chemical structure, buprenorphine is as effective as the opiates (e.g., morphine) in relieving pain but does not have the well-known physical dependence properties of the opiates and has a significantly greater margin of safety. See Joint Appendix on Appeal from the United States District Court (hereinafter "J.A.") at 117-18, 272-73.

By virtue of its synthesis, buprenorphine was initially regarded by FDA and the Drug Enforcement Administration ("DEA") as a "derivative" of thebaine, making it a Schedule II substance under 21 U.S.C. §812(c), Schedule II(a)(1) of the Controlled Substances Act ("CSA"). (J.A. 112-13, 274.) Schedule II controls are the most stringent that can possibly be applied to a drug with a legitimate medical use. 21 U.S.C. §812(b). However, the significant pharmacological differences between buprenorphine and the opiates (all of which are subject to very stringent controls) meant that, under the relative scheduling criteria of 21 U.S.C. 812(b), buprenorphine did not factually belong in Schedule II.[2] (*See* J.A. 112-13.) Until February 28, 1985, when DEA issued a final order placing buprenorphine in Schedule V, the factually inappropriate Schedule II status of the drug continued in effect. *See* 50 Fed. Reg. 8104 (February 28, 1985).

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[2] Indeed, by December 1981, buprenorphine had already been approved for marketing in a number of foreign countries—all of which had approved it as an uncontrolled drug.

II. Statutory Background

A. The Approval Requirements of the FFDCA

Buprenorphine HCl, the active ingredient in Buprenex, is a "new drug" as that term is defined by the Federal Food, Drug, and Cosmetic Act ("FFDCA") at 21 U.S.C. §321(p). Under 21 U.S.C. §355(a), every "new drug" must be the subject of an approved new drug application ("NDA") before it may be marketed legally in interstate commerce.

The NDA approval process involves the submission to FDA of an extensive application identifying the product and justifying its approval. *See* 21 C.F.R. §314.50 (J.A. at 271.) The application must include, *inter alia*, proposed "labeling" defining the conditions under which the product may safely and effectively be used. 21 C.F.R. §314.50(e)(2)(ii). The application must be supported by extensive chemical, pharmacological and toxicological data and include the results of controlled clinical (human) testing adequate to establish the safety and effectiveness of the product for use under the terms and conditions specified in that proposed labeling. 21 C.F.R. §314.50(d); 21 C.F.R. §314.125(b); 21 U.S.C. §355(d).

If an applicant's data meet the statutory standards of 21 U.S.C. §355(c)(1) and 355(d) and the labeling proposed by the applicant meets the requirements of the FDA regulations at 21 C.F.R. §201.56 and 201.57, FDA may approve the product for marketing. 21 C.F.R. §314.105(c). On the other hand, if the labeling proposed by the applicant is not adequately supported by the data contained in the application or does not otherwise meet the requirements imposed by the FFDCA and the implementing regulations, the application may simply be denied. 21 C.F.R. §314.120. Alternatively, the FDA may suggest to the applicant that additional data be submitted or that the applicant's proposed labeling be revised. If these conditions are met by the applicant, the NDA will then be approved.

21 C.F.R. §314.110. Under no circumstances, however, is FDA authorized to approve an application on terms different than those proposed or accepted by the applicant.[3]

B. The Interrelationship Between the FFDCA and the Status of a Drug Under the Controlled Substances Act

The regulation of a drug under the CSA is an integral part of the NDA approval process. First, FDA regulations specifically require that labeling for a prescription drug product include, when applicable, information on abuse potential and dependence liability as well as a statement of the drug's CSA status. 21 C.F.R. §201.57(h). Second, the FDA (in conjunction with its parent, the Department of Health and Human Services) plays a crucial role in the CSA scheduling or rescheduling of a drug. Under 21 U.S.C. §811(b), FDA has a primary responsibility in the initiation of a scheduling or rescheduling proceeding. (J.A. at 277-78.) Moreover, with respect to all medical and scientific matters, the FDA's recommendation as to the scheduling of a drug is binding on the DEA. 21 U.S.C. §811(b).

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[3] This procedure has been described by FDA most recently in the preamble to its final rule on premarket approval applications ("PMAs") for medical devices. *See* 51 Fed. Reg. 26341, 26357, paragraph 70 (July 22, 1986):

> An 'approval letter' reflects the agency's conclusion that important but easily resolved deficiencies exist in a PMA, and that FDA will approve the PMA if the applicant submits, and FDA finds acceptable, specific additional information or material identified in the letter or if the applicant agrees to other specific conditions identified in the letter . . . .
>
> The applicant may amend the PMA as requested, the course of action that most applicants probably will elect to follow. An applicant that is dissatisfied with the conditions stated in the 'approvable' letter may, however, elect to treat the 'approvable' letter as a denial of the PMA . . . .

This procedure is identical to that utilized by FDA in the processing of new drug applications. *See* 47 Fed. Reg. 46621, 46639, col. 2 (October 19, 1982).

FDA's responsibilities under the FFDCA and the CSA are closely interrelated, and the FDA must handle them simultaneously.[4] If FDA determines that a drug subject to a pending NDA requires more stringent scheduling, FDA will not permit the marketing of the drug until appropriate controls are implemented.[5] Similarly, if a drug is presently subject to more stringent controls than are appropriate, the product cannot be approved for market until there is: (a) an agreement between FDA and the applicant on the appropriate scheduling status to be reflected in the approved labeling, and, if necessary, (b) final DEA rulemaking placing the drug in the appropriate schedule.

III. The Approval of Buprenex

On October 31, 1979, after conducting extensive and costly clinical and preclinical investigations to test the safety and efficacy of the drug, Norwich submitted an

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[4] See the agency statement in its rescheduling recommendation (J.A. 113):

> In November, 1979, the Food and Drug Administration received a new drug application for buprenorphine. This action necessitated a reevaluation of the control status of this drug.

Indeed, the NDA itself must contain extensive data on the abuse potential of the drug so that FDA can assess the need for imposing greater or lesser controls under the CSA. See 21 C.F.R. §314.50(d)(5)(vii). The extensive data reviewed by FDA in its rescheduling recommendations for buprenorphine was part of the NDA submission for Buprenex. (J.A. 113-20.)

[5] *See* 51 Fed. Reg. 10190 (March 25, 1986), regarding the NDA approval and DEA scheduling of the drugs midazolam and quazepam. The drugs were not controlled under the CSA until the March 25, 1986 DEA order placed them into Schedule IV. As that order states:

> By letter dated March 3, 1986, the FDA notified DEA of the final NDA approval for each substance contingent upon the announcement of a final scheduling decision in the Federal Register. This final rule fulfills that scheduling condition for quazepam and midazolam.

51 Fed. Reg. 10190, 10191, col. 1.

NDA for Buprenex to the FDA pursuant to 21 U.S.C. §355. On January 16, 1981, Norwich amended the application, submitting revised proposed labeling that reflected the latest information pertinent to the prescribing and use of the drug. (J.A. 38-50.) This proposed labeling did not contain any information about the controlled status of the drug. This submission thus reflected the fact that the drug had been approved for marketing in a number of countries as an uncontrolled drug and that similar approval was sought by Norwich in the United States. That the agency recognized this as Norwich's position is reflected in the agency's October 14, 1981 response. (J.A. 52-55.)

The FDA's October 14, 1981 letter to Norwich took the form of an "approvable" letter, signed by Dr. Marion Finkel. (J.A. 320.) Dr. Finkel's letter noted that the Buprenex NDA could be approved contingent upon, *inter alia*, changes to the draft labeling that had last been submitted by Norwich in January 1981. None of Dr. Finkel's suggested changes addressed the scheduling status of the drug. However, in light of the fact that Norwich had proposed to label and market the drug as an uncontrolled product, and the agency's recognition that the existing Schedule II controls were inappropriately stringent for the drug, Dr. Finkel explicitly stated that Norwich "may not legally market the drug until final rulemaking procedures are enacted by the Drug Enforcement Administration." (J.A. 55.)

In late December 1981, Dr. Finkel telephoned Dr. Neill of Norwich to report that FDA was anxious to approve the Buprenorphine NDA before the end of the year and would do so if the conditions of her October 14, 1981 letter were met. As reflected in Dr. Neill's telephone report of his conversations with Dr. Finkel (J.A. 57), Norwich was able and willing to comply with all of the conditions of that letter except for matters relating to the still unresolved rescheduling of the drug.

Shortly thereafter, Dr. Finkel sent Norwich a letter dated December 29, 1981 indicating that "the application is approved." (J.A. 59.) However, rather than correctly reflecting Norwich's only outstanding labeling proposal, which was to market Buprenex as an uncontrolled drug, Dr. Finkel stated in her letter:

> As you know, the Division is preparing documents to effect lesser controls for Buprenorphine. This, however, in no way impairs your approval to market Buprenorphine in its current controlled substances schedule.

(J.A. 57.) This aspect of the "approval" had not been requested by Norwich, was completely unacceptable to it and was rejected.[6]

On January 27, 1982, in response to Dr. Finkel's December 29, 1981 letter (J.A. 61-77), Norwich did not submit Schedule II labeling but, instead, submitted revised draft labeling with the legend "C? (controlled drug schedule)." (J.A. 64, 65 and 66.)[7] The question mark reflected the unresolved status of buprenorphine as a controlled drug, as shown by the cover letter to this submission which explained that "when agreement has been reached, final printed labeling incorporating the appropriate controlled substances schedule will be submitted." (J.A. 61, 329.) Nor-

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[6] Norwich did not receive Dr. Finkel's December 29, 1981 letter until January 8, 1982. Thus, Norwich has argued in the alternative that, even if the Buprenex NDA were to be deemed approved prior to June 28, 1985, it could not be deemed approved prior to January 8, 1982—the earliest possible date on which Norwich could have known and accepted the agency's Schedule II labeling proposal. Approval of the Buprenex NDA between January 1, 1982, and September 24, 1984 would entitle Norwich to *ten* years of exclusivity—not five. 21 U.S.C. §355(j)(4)(D)(i).

[7] The controlled status of a drug under the CSA must be clearly shown on the label, in large print, by the legend "C-II," "C-III," "C-IV" or "C-V," as appropriate. 21 C.F.R. §1302.03(c). "C-II" reflects the most stringent controls, "C-V" the least. See 21 U.S.C. §812(b).

wich thus explicitly and unambiguously rejected the terms of FDA's December 29, 1981 purported "approval" of the Buprenex NDA.

Norwich's January 27, 1982 submission to the agency was followed by a letter from the president of Norwich, Mr. John M. Kolbas. In a February 3, 1982 letter to the Director of FDA's Bureau of Drugs, Richard J. Crout, M.D., Mr. Kolbas acknowledged the agency's December 29, 1981 letter. In so doing, however, he tactfully restated the company's rejection of the agency's proposal that Buprenex be labeled and marketed as a Schedule II drug and requested a meeting to "discuss the buprenorphine scheduling issue." (J.A. 107-08.)

On May 12, 1982, through the Assistant Secretary for Health of the Department of Health and Human Services, FDA forwarded to DEA a recommendation that buprenorphine be placed in Schedule V—the least stringent level of control short of total decontrol. (J.A. 112-21, 293.) On May 24, 1982, FDA rejected the draft labeling submitted by Norwich on January 27, 1982. (J.A. 79-81.) The agency called upon Norwich to incorporate a number of significant substantive changes in the draft labeling and concluded:

> Finally, we remind you of the labeling requirements under the Controlled Substances Act which will be necessary following control by the Drug Enforcement Agency [sic].

Thus, as of May 24, 1982, it was clear that there was no labeling under which the product could legally be marketed.

No further communications between FDA and Norwich concerning the text of the Buprenex labeling took place for the next two years. During this two-year period, the controlled status of buprenorphine was the subject of extensive DEA hearings requested by the patent holder of buprenorphine, Reckitt & Colman, Ltd. Reckitt & Colman

took the position in those hearings that the drug should be completely decontrolled—that even the FDA-proposed Schedule V controls were overly restrictive given the extremely limited abuse potential of the drug. See 50 Fed. Reg. 8104 (February 28, 1985).

During this period, Norwich provided to FDA quarterly, semi-annual and annual reports on the status of Buprenex in accordance with FDA reporting regulations. *See* 21 C.F.R. §310.300(b)(4)(i) (1981), now revised and recodified at 21 C.F.R. §314.80(c)(2). Submission of these reports in no way signified that Norwich believed it could legally market Buprenex during this time period. Indeed, Norwich explicitly stated in each of the reports under the heading "Current Package labeling" that labeling was "not approved." (J.A. 164-172.)

Even FDA recognized the significance of the lack of approved labeling. On August 2, 1984, an employee of Norwich wrote to the FDA and requested "a letter from the Food and Drug Administration stating that Buprenex (buprenorphine hydrochloride injectable) has been found to be safe and effective and approved by the agency for marketing within the United States." (J.A. 83.) This request went unanswered until December 5, 1984, when the Norwich employee received a telephone call from a member of the FDA Litigation and Recall Staff, stating that the requested letter could not be issued until the agency received copies of complete final printed labeling for the product. (J.A. 87.) Such labeling did not exist and thus, of course, could not be submitted. As a consequence, FDA did not issue the requested letter.

Finally, in February 1985, the scheduling status of buprenorphine was resolved. The Administrator of the DEA issued a final order placing buprenorphine in Schedule V. *See* 50 Fed. Reg. 8104 (February 28, 1985).

Between February and June 1985, Norwich and FDA negotiated over the content of the labeling for Buprenex.

Numerous substantive changes were suggested by both sides. (*See* J.A. 89-93.) In late June, an agreement was reached. Final printed labeling was approved by FDA on June 28, 1985. (J.A. 95.) Upon approval of Buprenex labeling, Norwich commenced marketing the drug in interstate commerce on June 29, 1985.

IV. Statutory Changes Affecting The Status of Buprenex

Prior to the 1984 amendments to the FFDCA, all new drug applications were required to contain "full reports of investigations which have been made to show whether or not [the] drug is safe for use and whether [the] drug is effective in use." 21 U.S.C. §355(b). Except with respect to copies of new drugs first approved prior to 1962, this requirement was consistently applied by FDA. This requirement severely limited the approval of generic copies of post-1962 new drugs because generic manufacturers were either unwilling or unable to expend the time and resources to generate the extensive safety and effectiveness data necessary to meet this standard.[8]

This regulatory scheme provided substantial competitive advantages to pioneer manufacturers of new drugs, and recognized the necessity of maintaining the incentives to develop new drugs, especially products that were not patented or would not have extensive patent life following FDA approval. As FDA stated in adopting regulations exempting safety and effectiveness data from disclosure under the Freedom of Information Act:

> If a manufacturer's safety and effectiveness data are to be released upon request, thus permitting

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[8] *See* H. Rep. 98-857, Part 2, 98th Cong., 2d Sess., p. 4. The consistent application of the "full reports" requirement to all NDA's was buttressed by the maintenance of all safety and effectiveness data submitted to FDA as "trade secrets" exempted from disclosure under the Freedom of Information Act. 21 C.F.R. §314.14 (1981) (revised and recodified at 21 C.F.R. §314.430 (1986)).

> 'me too' drugs to be marketed immediately, it is entirely possible that the incentive for private pharmaceutical research will be adversely affected.

39 Fed. Reg. 44602, 44634 (December 24, 1974).

The 1984 Amendments to the FFDCA permitted FDA to approve copies of previously approved drug products without the submission of "full reports of investigations" to prove the safety and effectiveness of the drug. New subsection (j) of §355 established criteria for approval of "abbreviated new drug applications" or ANDAs based only on manufacturing and bioequivalence data. 21 U.S.C. §355(j)(2)(A). Proof of safety and effectiveness for such applications is replaced by a simple reference to the approved pioneer drug product being copied. 21 U.S.C. 355(j)(2)(A)(i).[9]

The enactment of new §355(j) was a compromise between the desire to encourage availability of generic drugs and the need to preserve incentives for research-based pioneer manufacturers.[10] In partial fulfillment of the latter objective, §355(j) included five specific provisions guaranteeing pioneer manufacturers significant periods of non-patent exclusivity during which generic manufacturers cannot obtain effective approval of ANDAs. 21 U.S.C. §355(j)(4)(D).

This exclusivity was intended to provide pioneer manufacturers with adequate time to recover the extensive research and development costs which are associated with

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[9] FDA has not yet issued, or even proposed, any regulations implementing the provisions of new §355(j) although the 1984 amendments specifically required the promulgation of such regulations within one year of the statute's enactment. P.L. 98-417, Sec. 105(a). Until such regulations do issue, however, the amendments are self-executing. *Id.* at Sec. 105(b).

[10] *See Cong. Rec.* S10,503-4 (Aug. 10, 1984).

the development of any new drug whether it is protected by patent or not. Two provisions apply to first approvals of new chemical entities. The first, 21 U.S.C. §355(j)(4)(D)(i), provides ten years of exclusivity to new chemical entities first approved between January 1, 1982 and September 24, 1984 (the date of enactment of the 1984 amendments). The other provision establishes a five year period of exclusivity for new chemical entities approved subsequent to September 24, 1984. This provision, section 355(j)(4)(D)(ii), reads as follows:

> If an application submitted under subsection (b) for a drug, no active ingredient . . . of which has been approved in any other application under subsection (b) . . . is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) . . . .[11]

In other words, ANDAs for generic copies of new chemical entities first approved subsequent to September 24, 1984 may not be submitted to the FDA until five years after the date of the original approval of the pioneer drug.

V. The Proceedings Below

On August 6, 1985, counsel for Norwich submitted to Dr. Harry M. Meyer, Jr., M.D., Director, FDA Center for Drugs and Biologics, a request for recognition of the exclusivity afforded to Buprenex under the 1984 amendments. This request was based on Norwich's position that the drug had not effectively been approved, for purposes of the 1984 amendments, on December 29, 1981. Rather,

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[11] The remainder of this clause established different limitations in the case of an ANDA submitted as a challenge to the pioneer's patent. This additional language is not relevant to the instant case.

Norwich explained that, until complete labeling for the drug was approved on June 28, 1985, it did not have legal authority to market the product and, thereby, legal approval of its NDA. In response, agency officials suggested the request should be submitted as a "Citizen Petition." On August 19, 1985, Norwich resubmitted its request in the form of a "Citizen Petition." On December 4, 1985, FDA refused to recognize the exclusivity afforded to Norwich by the 1984 amendments. (Appendix C.)

The agency's position was, in sum, that the approval date is the date on which FDA sends a letter to the applicant stating that the application is approved. (App. C at 24a) It rested this decision on the bare statement contained in the December 29, 1981 letter that "the NDA is approved." It did not look behind the language of the letter to the actual facts and circumstances existing at the time of the letter.

On December 27, 1985, Norwich filed this action in the United States District Court for the Southern District of Ohio, seeking declaratory and injunctive relief to enforce its exclusivity rights under the 1984 amendments. The jurisdiction of the District Court was invoked under 28 U.S.C. §§1331, 1361 and 2201 in that the case arose under the Administrative Procedure Act, 5 U.S.C. §706, and the Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. §301 *et seq.*

On March 3, 1986, after a February 19, 1986 hearing on the merits, the District Court issued an order setting forth findings of fact and conclusions of law, ruling in favor of Norwich. (See Appendix B.) The Court found that appellants' position that Dr. Finkel's December 29, 1981 letter effectuated an approval of the Buprenex NDA was not supported in the administrative record. The Court's decision was based in part on the fact that Norwich's labeling submissions in 1981 did not describe the CSA schedule in which the substance was controlled, as required

by the FDA regulations at 21 C.F.R. §201.57(h)(1). The court also held that approval of the Buprenex NDA was contingent upon approval of labeling in its final form and, therefore, was not effective until June 28, 1985 when final labeling for the drug was approved. On this basis, the court held that the Buprenex NDA was entitled to five years of exclusivity pursuant to 21 U.S.C. §355(j)(4)(D)(ii).

On appeal, the Court of Appeals for the Sixth Circuit reversed (see Appendix A), deferring to FDA's analysis of the facts and the law.

REASONS FOR GRANTING THE WRIT

I. Introduction—The Precedential Significance of This Case

The issues raised in this matter are of great significance both to FDA[12] and to the pharmaceutical industry as a whole. The non-patent exclusivity provisions were a crucial and significant part of the compromise that led to enactment of the 1984 amendments. They were intended to provide defined and predictable periods of exclusivity to new and significantly improved drug products. In turn, the provisions were intended to assure continued incentives to invest in the time and resource-intensive research and development activities necessary to obtain FDA marketing approval for these important products. As interpreted by FDA, however, now with a deferential nod from the Sixth Circuit, these provisions are stripped of their intended thrust and have only such significance in an individual case as FDA chooses them to have.

FDA has already cited the Sixth Circuit decision in support of its position that a recently approved drug, "Versed"

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[12] FDA requested expedited briefing before the Court of Appeals in part because of its concern that the approval dates for drugs may be in doubt. (Motion of the Appellants for an Expedited Briefing Schedule, May 9, 1986.)

(midazolam hydrochloride) was "approved," for purposes of the 1984 amendments, when the agency issued an "approval" letter for the drug on December 20, 1985. *See* 52 Fed. Reg. 7035 (March 6, 1987). That "approval," however, was explicitly contingent on the scheduling of the drug by DEA *before* the drug was marketed. (*See* note 5, *supra*). The DEA scheduling notice on Versed was not published until March 25, 1986—over three months after FDA claims to have approved the drug. Thus, even though FDA prohibited marketing of the drug during that period of time, FDA has taken the position that the marketing exclusivity period under 21 U.S.C. §355(j)(4)(D)(ii) started running on December 20, 1985, effectively denying to the sponsor of Versed over three months of its exclusivity under 21 U.S.C. §355(j)(4)(D)(ii).[13]

FDA has also cited the Sixth Circuit decision in a similar case involving the drug "Cesamet" (nabilone), an uncontrolled drug that the agency purports to have approved on December 26, 1985. As with Versed, because of the abuse potential of Cesamet, FDA explicitly forbade the sale of the drug until conclusion of DEA scheduling proceeding. FDA did not even forward its scheduling recommendations to DEA, however, until April 25, 1986, and the drug has yet to be scheduled. *See* 51 Fed. Reg. 22085 (June 18, 1986). Thus, marketing of the drug has been delayed by FDA's own restrictions, for over 15 months so far. Nevertheless, citing the Sixth Circuit decision, FDA has officially declared that, for purposes of the 1984 amendments, the patent extension status of Cesamet is

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[13] The Versed matter has thus far arisen under Title II of the 1984 amendments. Title II provides for patent extensions for approved drug products based on the length of the so-called "regulatory review period" during which the drug was studied by its sponsor and the NDA reviewed by FDA. 35 U.S.C. §156. The "approval" of the product signals the end of the regulatory review period and, consequently, determines the length of the possible patent extension.

determined as of FDA's so-called "approval" letter of December 26, 1985. 52 Fed. Reg. 7214 (March 9, 1987).[14]

Similarly, the United States District Court for the District of Columbia has cited the Sixth Circuit decision in support of a January 27, 1987 decision in the case of *Mead Johnson Pharmaceutical Group v. Bowen*, Civ. No. 85-3971. That case, involving the drug product "Desyrel" (trazodone hydrochloride), arises under 21 U.S.C. §355(j)(4)(D)(i) which provides ten years of exclusivity to new drugs approved between January 1, 1982 and September 23, 1984. FDA claims, and the District Court has deferred to the agency's position, that Desyrel was approved on December 24, 1981. This is so even though the Desyrel approval explicitly required the submission of revised printed labeling before the product could be marketed--an event that did not occur until 1982.[15]

These cases serve to illustrate how the exact "approval" date of an NDA, once regarded as largely inconsequential, has become of crucial importance under the 1984 amendments in fixing the exclusivity and patent extension rights of the sponsor of a new drug product. They also illustrate the fact that, under FDA's definition of "approval," deferred to by the Court of Appeals, FDA can unilaterally limit or even eliminate the property rights (NDA exclusivity and/or patent extension) which Congress intended to grant to the originators of new drug products by passage of the 1984 amendments. Finally, they illustrate why deference to FDA's position in the case of Buprenex is unwarranted.

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[14] See also the case of "Dormalin" (qazepam hydrochloride) in which FDA has cited the Sixth Circuit decision for the same purpose and to the same effect. 52 Fed. Reg. 6221 (March 2, 1987).

[15] The Desyrel case has been appealed by Mead Johnson to the Court of Appeals for the District of Columbia Circuit. The Versed Cesamet and Dormalin matters are still pending before FDA and the Patent and Trademark Office.

II. THE COURT OF APPEALS IMPROPERLY CONCLUDED THAT FDA'S DEFINITION OF "APPROVAL" IS CONSISTENT WITH THE STATUTORY AND REGULATORY STANDARDS

FDA's position in this matter rests on a single regulation which defines the approval date of an NDA as the date on which FDA sends the applicant a letter saying that the NDA is "approved." 21 C.F.R. §314.105 (1981), revised and recodified at 21 C.F.R. §314.105(a) (1986). Despite FDA's tautological definition, there are numerous statutory and regulatory prerequisites to proper, effective approval of an NDA—all of which must be satisfied before an NDA can be considered legally approved. FDA's definition of the date of approval is thus facially inadequate to answer the substantial legal questions raised by the instant case and other cases arising under the 1984 amendments.

As explained in the Statement of the Case, above, at §II.A., the approval of a new drug application entails an affirmative FDA conclusion that the drug in question has been proven to be safe and effective for use under the specific labeling which is proposed to accompany the drug and provide complete instructions for its use. FDA regulations outline in great detail the content and format of the labeling which is required for prescription drugs. 21 C.F.R. §201.57. *Inter alia*, the regulations require labeling of a drug subject to CSA control to include a description of the drug's scheduling status. 21 C.F.R. §201.57(h)(1). Throughout December, 1981, Norwich's proposed labeling for Buprenex did not include a description of its CSA status.

The omission of scheduling information from the proposed Buprenex labeling, as is clearly reflected in the administrative record (J.A. 38-50, 52-55) and unrebutted by the government, was a crucial aspect of Norwich's application. Norwich simply had not sought and did not accept

an approval to market Buprenex as a Schedule II drug. Every document in the Administrative Record other than the December 29, 1981 "approval" letter and FDA's similarly self-serving listing of buprenorphine as an "approved" drug in its December 1981 listing of Approved Prescription Drug Products[16] confirms that simple fact.

Recognition that the December 29, 1981 letter did not properly effectuate an approval of the Buprenex NDA is confirmed by: (a) the January 27, 1982 submission by Norwich of draft labeling with the legend "C?" instead of "C-II" and explicitly stating that this aspect of the labeling could not be resolved until "agreement has been reached" (J.A. 61-77); (b) the February 3, 1982 letter from the president of Norwich to the Director of FDA's Center for Drugs and Biologics confirming that the terms of the FDA's December 29, 1981 letter were not acceptable to Norwich (J.A. 107-08); (c) the May 24, 1982 FDA letter rejecting the January 1982 Norwich submission of draft labeling and asserting that final labeling would have to reflect DEA action on the FDA's May 12, 1982 rescheduling recommendation (J.A. 79-81); (d) the periodic reports submitted by Norwich with respect to the Buprenex NDA which consistently stated "not approved" under the heading "Current Package Labeling" (Defendants' Memoran-

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[16] FDA continued to list Buprenex in its Approved Prescription Drug Products list through the 5th Edition (July 1984). It was deleted, however, in the supplements to the 5th Edition. FDA has claimed that this deletion was based on the fact that the product was not being marketed. Of course, FDA was fully aware at all times that the drug had *never* been marketed. On FDA's theory, therefore, the drug should never have been listed. On the other hand, when FDA finally did delete its listing of Buprenex, the statutory requirements under the 1984 amendments required the listing of all approved drugs, whether marketed or not. 21 U.S.C. §355(j)(6)(A)(i)(I). The obvious implication of the deletion is thus exactly the opposite of that suggested by FDA. When FDA's list of approved drugs gained new legal significance under the 1984 amendments, Buprenex was deleted in order to avoid the erroneous implication that the product was approved.

dum of February 11, 1986, Exhibit D); and (e) FDA's 1984 refusal to certify that Buprenex could legally be sold in the United States without the submission of complete labeling for the drug—labeling which, of course, did not exist. (J.A. 83-87.)

As found by the District Court, the administrative record contains no support for the position that the FDA's December 29, 1981 letter effectuated an actual legal approval of the drug. Rather, the record establishes that the proposed labeling submitted by Norwich to the agency did not incorporate a specific CSA status but, instead, represented a proposal that could not be effectively approved by the agency until the drug was decontrolled or until agreement was reached on a proper schedule for the drug. As of December 29, 1981, neither event had occurred. The purported approval of the Buprenex NDA on December 29, 1981 was inconsistent with FDA's own regulations which required that the labeling of an approved drug product reflect its CSA status (21 C.F.R. §201.57(h)(1)) and be publicly available at the time of approval (21 C.F.R. §314.10 (1981)). The government's position that the December 29, 1981 letter constitutes the "approval" of Buprenex is thus arbitrary, capricious and not in accordance with law.

The Court of Appeals appears to have missed the point of this argument thus:

> . . . [T]he District Court's finding that the FDA's actions violated 21 C.F.R. 201.57(h)-(1) seems to ignore that buprenorphine hydrochloride *was* scheduled in December, 1981, although not under the classification desired by Norwich. Thus, the FDA approved Buprenex as a Schedule II drug . . .

(App. A at 8a) (emphasis in original). That buprenorphine was scheduled at that time is not in dispute. However, as outlined above, the application before the agency in De-

cember 1981 simply did not permit FDA to issue such an approval. The proposed labeling before the agency did not provide for Schedule II classification, Norwich did not accept Schedule II labeling and, indeed, as reflected even in the December 29, 1981 letter itself, FDA recognized that Schedule II labeling would not accurately reflect the abuse potential of the drug.

The implication of the Court of Appeals decision in this regard is that FDA has authority unilaterally to approve a drug with different indications for use or restrictions on use than were proposed by the applicant. For example, FDA could approve a potent analgesic like buprenorphine for the treatment of very limited types of pain even though the application requests approval for use in all types of moderate to severe pain. Under 21 C.F.R. §314.110, FDA can *suggest* that an applicant narrow the scope of its proposed uses for a product to those uses that FDA would be willing to accept. But FDA cannot, however, simply impose such limitations, claim that the application is approved, and go on to other matters. *See* Statement of the Case, above, at §II.A.. The Court of Appeals decision thus provides troublesome authority for FDA to approve drugs on terms which please the agency but which are unacceptable to the applicant. In fact, it places FDA in a position to coerce an NDA applicant into accepting FDA's terms by simply calling a drug "approved" and thereby prematurely starting the exclusivity time clock running before there has been final agreement as to the terms and conditions under which the drug will be marketed, i.e., its final labeling. Such broad authority serves no regulatory purpose (although it may serve a bureaucratic one)—and it is inconsistent with the clear intent and purpose of the FFDCA, the 1984 amendments and the implementing regulations.

Finally, in the absence of approved complete and final labeling, the December 29, 1981 letter could, at best, constitute a "contingent" approval of the NDA. This is re-

flected in the regulations quoted in this regard by the District Court (App. B at 19a.) *See* 21 C.F.R. §314.1(c)(2), item 4.e. (1981) and 21 C.F.R. §314.100(d) (1981). It is true, as pointed out by the Court of Appeals, that these particular regulations speak in terms of the "ordinary" situation and therefore can be read to allow for exceptions. However, other agency regulations and pronouncements confirm that FDA intended that approval of complete, final labeling was always to be required, at least until late 1982. The regulations at 21 C.F.R. §314.10 (1981) require FDA, upon approval of an NDA, to place on public file "the approved labeling." Moreover, the agency itself stated that an October 1982 proposal to provide for the approval of NDAs based solely on complete *draft* labeling represented an "important change" in agency procedures. 47 Fed. Reg. 46621, 46639, col. 1 (October 19, 1982).

It is undisputed that final printed labeling for Buprenex was approved for the first time on June 28, 1985. Prior to this time, there was no approved labeling which could have been put on public file. Again, this reflects that, for purposes of the 1984 amendments, the approval of the Buprenex NDA took place on June 28, 1985. For all of these reasons, the District Court correctly found that the government's position in this matter is unsubstantiated in the record, arbitrary and capricious and not in accordance with law. The Court of Appeals' reversal of that determination was unwarranted, even under such a deferential standard of review.

III. THE COURT OF APPEALS APPLIED AN IMPROPERLY DEFERENTIAL STANDARD OF REVIEW TO FDA'S POSITION IN THIS CASE

The application of a highly deferential standard of review by the Court of Appeals in this case was inconsistent with both the Administrative Procedure Act and the requirements of due process in that 1) FDA failed to apply essential procedural safeguards necessary to assure full

and fair consideration of Norwich's claim of exclusivity; 2) FDA brought no significant expertise to bear in opposing the exclusivity claim and 3) FDA was institutionally incapable of considering Norwich's claim in an impartial manner.

A. Failure to Follow Essential Procedural Safeguards

The courts are entitled, indeed required, to conduct a *de novo* review of agency action in cases, such as this, where the action of an agency "is adjudicatory in nature and the agency's fact-finding procedures are inadequate." *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 415 (1971); *see also Camp v. Pitts*, 411 U.S. 138, 141-2, (1973). The District Court found it unnecessary to conduct such a review because it found FDA's position to be arbitrary, capricious and contrary to law. The Court of Appeals, however, in deferring to FDA under this standard, side-stepped its responsibility in this regard.

The fact-finding procedures utilized by the FDA in the present case were woefully inadequate. The agency's December 4, 1985 letter (Appendix C) shows that the agency made no effort to investigate or consider facts within the knowledge of agency personnel, and which should have been reflected in agency records, that corroborate Norwich's view of the circumstances surrounding the late 1981 and early 1982 agency actions on the Buprenex NDA.[17] The inadequacy of the agency's fact-finding procedures is

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[17] Documents in Norwich's files reflect numerous contacts between FDA and Norwich regarding the Buprenex NDA during the 1981-82 time period. (*See* J.A. 338, 340-44, 351-57, 405, 406.) FDA regulations at 21 C.F.R. §§10.65(d)(3) and 10.65(f)(2) require that important meetings (including telephone conversations, *see* 21 C.F.R. §10.3(a)) between agency personnel and members of the public be summarized in writing by the agency personnel involved. No such summaries of any of the conversations documented in the Norwich files were included by government counsel in its administrative record.

also reflected in the improper maintenance and preparation of its so-called "administrative record."[18]

Finally, the agency made no attempt to provide important due process safeguards in the processing of Norwich's Citizen Petition, such as an opportunity for Norwich to comment on the agency's tentative position before it reached a final decision. Such safeguards are essential prerequisites to deferential review of "agency action." *See Zotos International, Inc. v. Kennedy*, 460 F. Supp. 268 (D.D.C. 1978) (cited with approval in *Carson Products Co. v. Califano*, 594 F.2d 453, 457-9 (5th Cir. 1979); *see also NOW, Washington, D.C. Chapter v. Social Security Administration*, 736 F.2d 727, 738-40 (D.C. Cir. 1984)) and *Del Laboratories, Inc. v. United States*, 86 F.R.D. 676 (D.D.C. 1980). Under these circumstances, deferential review of the agency's position was improper. *Montgomery Imp. Ass'n. Inc. v. U.S. Dept. of HUD*, 543 F. Supp. 603 (M.D. Ala. 1982), *aff'd*, 645 F.2d 291 (5th Cir. 1981).

B. Lack of Applicable Agency Expertise

Deference was also improper because FDA has no expertise in applying the standards for non-patent exclusivity. Indeed, exclusivity did not even exist under the FFDCA until enactment of the 1984 amendments. Moreover, in violation of the statutory command, FDA has even as of the date of submission of this petition failed to propose, let alone adopt, regulations pertaining to the granting or denying of exclusivity under the 1984 amendments.[19] Thus, there has been no opportunity for the agency to

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[18] FDA regulations specify that the administrative record on a Citizen Petition "closes on the date of the Commissioner's decision unless some other date is specified." 21 C.F.R. §10.30(j). The record in this proceeding, however, was supplemented by government counsel over two months after the December 4, 1985 decision (Appendix C), clearly violating both the letter and the intent of the regulation.

[19] *See* note 9, above.

develop expertise with respect to this new law on the basis of full and open public notice and comment.[20]

This is particularly so with respect to the question raised in the instant case as to the date of approval of the Buprenex NDA for purposes of the 1984 amendments. Technical, scientific expertise of the agency is not required to determine the meaning of "approval" as used by Congress in granting periods of exclusivity. *See Genstar Chemical Ltd. v. ICC*, 491 F. Supp. 391, 396 (D.D.C. 1980), *rev'd on other grounds*, 665 F.2d 1034 (D.C. Cir. 1981), *cert. denied*, 456 U.S. 905 (1982); *see also FTC v. Motion Picture Advertising Service Co.*, 334 U.S. 392, 404-5 (1953). The District Court was fully competent to interpret the word "approval" as used in the 1984 amendments. As the Tenth Circuit has stated:

> When the administrative interpretation is not based on expertise in the particular field, however, but is based on general common law principles, great deference is not required.

Jicarilla Apache Tribe v. Fed. Energy Reg. Comm., 578 F.2d 289, 292-3 (10th Cir. 1978).

Moreover, this decision did not arise out of "the sort of long-standing, clearly articulated interpretation of the statute which would be entitled to great judicial deference . . . ." *Federal Maritime Comm. v. Seatrain*, 411 U.S. 726, 745 (1973). Prior to 1984, there was no reason or occasion for the agency to give serious consideration to the question of whether an NDA was properly approved in the absence of complete and properly approved labeling.

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[20] Indeed, according to a speech by James C. Morrison, Deputy Director, Office of Drug Standards, FDA, presented to a Food and Drug Law Institute conference in Washington, D.C. on December 9, 1986, the agency has "abandoned the mythology of a projected date [for the promulgation of regulations], and we just hope that someday within our lifetime they will be published."

In addition, the agency's interpretation of the FFDCA is not entitled to deference because it is inconsistent with the undisputed Congressional purpose in 1984 of assuring periods of "exclusive market life" for new pioneer drug products.[21]

> [T]he existence of a prior administrative practice, even a well-explained one, [does not] relieve us of our responsibility to determine whether that practice is consistent with the agency's statutory authority.

SEC v. Sloan, 436 U.S. 103, 118 (1978). As the Supreme Court stated in the often-quoted case of *NLRB v. Brown*:

> Reviewing courts are not obliged to stand aside and rubber-stamp their affirmance of administrative decisions that they deem inconsistent with a statutory mandate or that frustrate the congressional policy underlying a statute. Such review is always properly within the judicial province, and courts would abdicate their responsibility if they did not fully review such administrative decisions.

NLRB v. Brown, 380 U.S. 278, 291-2 (1965); *see also Volkswagonwerk v. Federal Maritime Comm.*, 390 U.S. 261, 272, *modified on other grounds*, 393 U.S. 901 (1968); *Morton v. Ruiz*, 415 U.S. 199, 232 (1974).

Significant in this regard are the agency's proposed rules to implement its responsibilities under Title II of the 1984

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[21] The House Committee on Energy and Commerce, reporting on an earlier version of the amendments which contained the ten year exclusivity provision, stated its intention that drugs coming under the provision receive "ten years of exclusive market life." (H. Rep. 98-857, Part 1, 98th Cong., 2d Sess., page 15.) Congressman Waxman, the key House sponsor of the 1984 amendments, during the House debate on the final version of the bill, specifically referred to all of the finally-adopted exclusivity provisions as affording periods of "exclusive market life." *Cong. Rec.* H9, 113-4 (Sept. 6, 1984).

amendments—provisions relating to patent term restoration. Significant property rights, such as the length of a patent extension under Title II of the amendments, turn on the date of approval of the patented drug product. Thus, in the preamble to these proposed rules, FDA recognized that "approval" letters such as that issued on December 29, 1981 in the case of Buprenex, which leave significant, substantive issues unresolved with respect to labeling and marketing of the drug product, are inappropriate in light of the 1984 amendments. In the agency's own words:

> . . . for human drug products, an approval letter will be issued when the only conditions which must be met prior to marketing relate to minor editorial labeling deficiencies . . . and will signify approval of a marketing application; while an "approvable" letter . . . (which requires the applicant to take further substantive actions to meet certain conditions or supply additional information prior to marketing) will not signify approval.

51 Fed. Reg. 25338, 25341, col. 1 (July 11, 1986). The clear implication of these statements is that, in order to properly carry out the intent of Congress in the 1984 amendments, FDA must not issue premature approvals, such as the December 29, 1981 "approval" of Buprenex.[22] Deference due to an administrative position depends on the consistency of the position with "earlier and later pronouncements" of that agency. *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944). Thus, no deference is due in the present case.

C. Bias Inherent in the Agency's Decision

Deference to the agency in this case is particularly inappropriate since it involves the agency's uncritical review

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[22] The reasoning and policy concerns behind this proposal are as applicable under the 1984 exclusivity provisions as they are under the patent extension provisions of the 1984 amendments.

of its own conduct. As found by the district court, the agency was ignoring its own regulations in purporting to "approve" the Buprenex NDA in 1981 and thus failed to effectuate actual legal approval of that NDA. Nevertheless, the agency took credit for the approval by publicly announcing (at a time when approval dates had no ramifications with respect to exclusivity or patent extension) that it had approved a record number of NDAs in 1981.[23] It is unreasonable to expect that FDA would willingly admit that it had acted improperly or ineffectually under these circumstances. Instead, its 1985 decision in this matter was simply an attempt to justify post hoc its 1981 actions. This attempt did not and could not provide an impartial analysis as to whether the December 1981 "approval" of Buprenex actually constituted a legal approval of the drug under the proper statutory and regulatory standards.

Norwich is entitled to a fair hearing, before an impartial decisionmaker, on its claim to exclusivity rights with respect to Buprenex. Indeed, as this Court has stated, "our system of law has always endeavored to prevent even the *probability* of unfairness." *In re Murchison*, 349 U.S. 133, 136 (1955) (emphasis added). Therefore, a flexible approach must be used in assessing the potential partiality of a decisionmaker: "Circumstances and relationships must be considered." *Id.* "[The Court] should be alert to the possibilities of bias that may lurk in the way particular procedures actually work in practice." *Withrow v. Larkin*, 421 U.S. 35, 54 (1975). Although, in the present case, FDA may have no particular bias against Norwich, it does not qualify as an impartial decisionmaker since "it is biased with respect to the factual issues to be decided . . . ." *Miller v. City of Mission, Kansas*, 705 F.2d 368, 372 (10th Cir. 1983).

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[23] Twenty-six percent of this record number of "approvals" were issued in the last 11 days of the year. FDC Reports 44:2, January 11, 1982, p. 16.

Under such circumstances, it is imperative that the Courts not defer to the agency's position. Rather, the Courts must provide the full review of the facts and the impartial decisionmaking process lacking at the agency level in this case. See *Pickering v. Board of Education*, 391 U.S. 563, 578 n.2 (1968).[24]

CONCLUSION

For the foregoing reasons, the Petitioner, Norwich Eaton Pharmaceuticals, Inc., prays that this Honorable Court grant the instant Petition for Writ of Certiorari and, upon review, reverse the decision of the Sixth Circuit Court of Appeals, and reinstate the Order of the District Court for the Southern District of Ohio rejecting respondents' interpretation of the effect of its December 29, 1981 so-called "approval" of Buprenex on the exclusivity afforded the product under the 1984 amendments.

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[24] As the Court stated in *Pickering*,

> We do not propose to blind ourselves to the obvious defects in the fact-finding process occasioned by the board's multiple functions .... Accordingly, since the state courts have at no time given *de novo* consideration to [the evidence] ..., we feel free to examine the evidence in this case completely independently and to afford little weight to the factual determinations made by the Board.

Id. See also Porter v. Califano, 592 F.2d 770, 783 (5th Cir. 1979), citing *Pickering* and holding that "the stricter standard of review generally applicable to the fact-finding and conclusions of a less than impartial tribunal" is also applicable in review of agency action under the APA.

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April 9, 1987

APPENDIX

APPENDIX A

NORWICH EATON PHARMACEUTICALS, INC.,
Plaintiff-Appellee,

v.

OTIS R. BOWEN, Secretary of Health and Human Services; FRANK E. YOUNG, M.D., Ph.D., Commissioner of Food and Drugs; UNITED STATES FOOD AND DRUG ADMINISTRATION,
Defendants-Appellants.

No. 86-3397.

UNITED STATES COURT OF APPEALS, SIXTH CIRCUIT.

808 F.2d 486

Argued Nov. 10, 1986
Decided Jan. 9, 1987.

Before: KENNEDY and NORRIS, Circuit Judges; and CONTIE, Senior Circuit Judge.

KENNEDY, Circuit Judge.

Defendants-appellants Otis R. Bowen, Secretary of Health and Human Services, *et al.* ("the Government") appeal from a judgment for plaintiff-appellee Norwich Eaton Pharmaceuticals, Inc. ("Norwich") in an action seeking a declaration of rights under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-392 ("FFDCA"). The Government argues that the District Court exceeded the appropriate scope of review and that the District Court erroneously found that the Food and Drug Administration's ("FDA") denial of Norwich's citizen petition was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. We find that the District Court

reviewed the agency action under the appropriate standard, but we reverse its determination that agency's action was invalid.

I.

Norwich is licensed by Reckitt and Colman, Ltd., an English pharmaceutical company, to distribute buprenorphine hydrochloride in the United States under the trade name Buprenex Injectible ("Buprenex"). Buprenex is a new analgesic drug used for treatment of moderate to severe pain. Because it is derived from the opiate thebaine, buprenorphine hydrochloride is a narcotic drug subject to control by the Drug Enforcement Administration ("DEA") under the Controlled Substances Act, 21 U.S.C. § 801 *et seq.* ("CSA"). As a derivative of thebaine, buprenorphine hydrochloride originally was automatically classified as a Schedule II substance under the CSA, which meant that it was subject to the most stringent controls applicable to a drug with legitimate medical use. Because of its unique molecular structure, however, buprenorphine hydrochloride does not have the physical dependence properties of the other opiates. This led to its reclassification in 1985 as a Schedule V drug, which is the lowest level of control short of decontrol.

On October 31, 1979, Norwich filed a New Drug Application ("NDA") with the FDA for Buprenex. At that time, buprenorphine hydrochloride had not been approved for marketing in the United States. On October 14, 1981, Dr. Marion Finkel of the FDA sent Norwich a letter stating that the NDA would be approved if Norwich made certain changes in the labeling. Dr. Finkel also stated that the drug was not marketable until the DEA had completed its final rulemaking procedures. At that time, efforts were underway before the DEA to reclassify the drug from Schedule II to Schedule V of the CSA.

On December 29, 1981, Dr. Finkel sent a second letter to Norwich, in which she stated:

> We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the labeling. As discussed in a telephone conversation between Dr. Alexander Neill and Dr. Marion J. Finkel on December 22, 1981, you have agreed to the conditional Phase IV bioavailability study and the labeling revisions outlined in our October 14, 1981 letter. Accordingly, the application is approved.
>
> As you know, the Division is preparing documents to affect lesser controls for buprenorphine. This, however, in no way impairs your approval to market buprenorphine in its current controlled substances schedule.

Joint Appendix at 59 (emphasis added).

On January 27, 1982, Norwich submitted revised draft labeling to the FDA. On February 3, 1982, John M. Kolbas, the president of Norwich, sent a letter to the FDA acknowledging that the FDA had "approved" Buprenex and noting that the drug was currently subject to Schedule II controls. The letter stated further: "Although the letter approving the Buprenex NDA indicated that we may market the product under Schedule II controls, there are many factors which adversely affect the feasibility of this option." *Id.* at 383. Kolbas requested a meeting regarding the scheduling issue. On May 24, 1982, the FDA sent a letter to Norwich acknowledging receipt of Norwich's "supplemental application" providing for labeling changes and requesting additional changes in the label. Norwich submitted further labeling changes in September, 1984 and February and March, 1985. On February 28, 1985, the DEA ruled that buprenorphine hydrochloride was a Schedule V Narcotic Controlled Substance. On June 20, 1985, the FDA made its last request for changes in the labeling. On June 24, 1985, the FDA received final printed labeling from Norwich. On June 28, 1985, the labeling was ap-

proved. Norwich began marketing Buprenex on June 29, 1985.

Meanwhile, the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, Stat. 1585 (amending 21 U.S.C. § 355) ("the Act"), became law on September 24, 1984. Title I of the Act is intended "to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." H.R. Rep. No. 857, Part I, 98th Cong., 2d Sess. 14, *reprinted* in 1984 U.S. Code Cong. & Ad. News 2647, 2647. In addition, Title I provides a limited period of protection from competition to certain previously approved pioneer drugs by granting non-patent marketing exclusivity of ten years to new chemical entities approved on or after January 1, 1982 and on or before September 24, 1984, *see* 21 U.S.C. § 355(j)(4)(D)(i), (c)(3)(D)(i), and non-patent marketing exclusivity of five years to drugs approved after September 24, 1984, see 21 U.S.C. § 355(j)(4)(D)(ii), (c)(3)(D)(ii). Title II provides an incentive for pioneer drug research by "restor[ing] . . . some of the time lost on patent life while the product is awaiting pre-market approval." H.R. Rep. No. 857, Part I, *supra*, at 15, *reprinted* in 1984 U.S. Code Cong. & Ad. News at 2648.

On August 19, 1985, Norwich filed a petition with the FDA seeking a declaration that Buprenex was entitled to exclusivity in marketing. Norwich argued that at the time of the 1981 "approval" there was no approved label under which the drug could have been marketed; thus, there was no valid approval. Norwich contended that approval actually came when the final printed label was submitted to the FDA in June, 1985. Norwich argued in the alternative that the approval became effective on January 8, 1982, which was the date on which Norwich received the FDA's letter of December 29, 1981. The FDA provided a detailed response denying this petition and stating that Buprenex had been approved on December 29, 1981, before the statutory date allowing exclusivity.

Norwich brought suit in the United States District Court for the Southern District of Ohio. The District Court held that Buprenex was not approved on December 29, 1981, but rather on June 28, 1985, the date on which the FDA approved an application for labeling that contained a Schedule V designation under the CSA. The Government appeals.

II.

The Government first raises a procedural issue; i.e., that the District Court went beyond the administrative record in reviewing the agency's action. The District Court was required to review the agency's decision that Buprenex was approved in 1981 to determine whether that decision was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," as specified in 5 U.S.C. § 706(2) (A). The scope of review under this section is narrow: "In applying that standard, the focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court." *Camp v. Pitts*, 411 U.S. 138, 142 (1973). The Government asserts that the District Court erroneously conducted a trial *de novo* when it reviewed the FDA's action.

As this Court recently noted in *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir. 1982), *de novo* review of agency action is the exception rather than the rule, unless required by statute. " '[*D*]*e novo* review is appropriate only where there are inadequate factfinding procedures in an adjudicatory proceeding, or where judicial proceedings are brought to enforce certain administrative actions.' " *Id.* at 483 (*quoting Camp v. Pitts*, 411 U.S. 138, 141 (1973)).

The District Court did not conduct a trial *de novo* here. The District Court did admit evidence not in the administrative record. The Government objected, and the District Court responded that it could not determine whether the

administrative record was adequate without seeing the document that Norwich was offering. As the Ninth Circuit has recognized:

> It will often be impossible, especially when highly technical matters are involved, for the court to determine whether the agency took into consideration all relevant factors unless it looks outside the record to determine what matters the agency should have considered but did not.

Asarco, Inc. v. EPA, 616 F.2d 1153, 1160 (9th Cir. 1980). Thus, consideration of evidence outside the administrative record is proper under some circumstances, *e.g.*, "for background information . . . or for the limited purposes of ascertaining whether the agency considered all the relevant factors or fully explicated its course of conduct or grounds of decision." *Id.* (citation omitted).

Moreover, the District Court stated in its Order that it based its decision upon its "review of the administrative record, the memoranda and the arguments by counsel." Joint Appendix at 263. The Order does not reveal that the District Court used any evidence outside the administrative record in reaching its decision. Thus, we find that the District Court did not conduct a trial *de novo* and that the Government's contention that the District Court based its decision on information outside the administrative record is without merit.

III.

On the merits, the Government appeals from the District Court's determination that Buprenex was not approved until June 28, 1985. We begin by noting that the proper issue for this Court to address, as it was for the District Court, is whether the FDA's determination on December 6, 1985 that Buprenex had been approved on December 29, 1981 was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

The District Court found that the Secretary's decision that the December 29, 1981 letter constituted final approval of the Buprenex NDA was contrary to law because the FDA could not approve a drug before it received final printed labeling. Therefore, the Court concluded that the approval date was June 28, 1985, which is the date that the FDA approved the final printed labeling permitting sale of Buprenex as a Schedule V drug. Adoption of this date would give Norwich a 5-year exclusivity period. *See* 21 U.S.C. § 355(j)(4)(D)(ii), (c)(3)(D)(ii).

We cannot agree with the District Court's characterization of the law. We see nothing in either the statute or the regulations which would prohibit the FDA from approving a drug based upon proposed labeling as it purported to do in December, 1981.

The District Court began by noting that 21 U.S.C. § 355(b) requires the sponsor of a new drug to submit "specimens of the labeling proposed to be used for such drug" in its NDA before the application will be considered.[1] The Court also quoted 21 C.F.R. § 201.57(h)(1),[2] which requires that the schedule of a drug controlled by the DEA be stated in the labeling. The Court found that the DEA did not issue its final rule on the scheduling of buprenorphine hydrochloride until February 28, 1985, and that Norwich's label submissions before that date were thus insufficient to allow approval. The District Court also relied on 21 C.F.R. § 314.1(c)(4)(e) in finding that the FDA had a stated policy not to approve an NDA until the labeling was in its final form. This regulation, in its 1981 version, stated: "An application will not ordinarily be approved prior to the submission of the final printed label and labeling of

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[1] This requirement was present in the version of the FFDCA in effect in 1981 and was not changed by the 1984 Act. See 21 U.S.C. § 355(b)(6) (1976); 21 U.S.C. § 355(b)(1)(F) (Supp. III 1985).

[2] This language of this regulation remained the same from 1981 through 1986.

the drug." 21 C.F.R. § 314.1(c)(4)(e) (1981). The District Court thus concluded that the FDA's letter of December 29, 1981 merely indicated Buprenex's "approvable" status under 21 C.F.R. § 314.100(d)[3] and that "the FDA's 'approval' of the Buprenex NDA was contingent upon and not effective until approval of labeling in its final form." Joint Appendix at 264.

We disagree. The FDA's interpretation that it was authorized in 1981 to approve a drug before final labeling was submitted does not conflict with the statute then in effect. Both the version of section 355(b) in effect in 1981, see 21 U.S.C. § 355(b)(6) (1976), and the amended version, see 21 U.S.C. § 355(b)(1)(F) (Supp. III 1985), require submission of "specimens of the labeling proposed to be used for such drug," but do not specifically require submission of the final labeling. Thus, the statute cannot be read to require submission of final printed labeling before approval. Nor do the regulations mandate this conclusion. The use of the word "ordinarily" in 21 C.F.R. § 314.1(c)(4)(e) (1981) logically implies that on some occasions the FDA will approve an application based on draft labeling. Moreover, the District Court's finding that the FDA's actions violated 21 C.F.R. § 201.57(h)(1) seems to ignore that buprenorphine hydrochloride was scheduled in December, 1981, although not under the classification desired by Norwich. Thus, the FDA approved Buprenex as a Schedule II drug in December, 1981, subject to Nor-

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[3] This regulation stated:

> On the basis of preliminary consideration of an application or supplemental application containing type-written or other draft labeling in lieu of final printed labeling, an applicant may be informed that such application is approvable when satisfactory final printed labeling identical in content to such draft copy is submitted.

21 C.F.R. § 314.100(d) (1981).

wich's compliance with the agreed-upon changes in the draft label.[4]

Because of its conclusion that approval did not come until June 28, 1985, the District Court did not address Norwich's alternative contention that the approval contained in the letter dated December 29, 1981 became effective on January 8, 1982, which is the date on which Norwich received the letter. If Norwich is correct, Buprenex is entitled to a 10-year exclusivity period. See 21 U.S.C. § 355(j)(4)(D)(i), (c)(3)(D)(i). We find that this interpretation is not mandated by the statute or the regulations.

The FDA regulation in effect at the time the letter was sent stated that "the application shall be approved on the date of the notification." 21 C.F.R. § 314.105 (1981). (The FDA has since amended the regulation to specifically provide that "[t]he date of the agency's approval letter is the date of approval of the application." 21 C.F.R. § 314.105(a) (1986).) The FDA interprets the 1981 regulation as meaning that approval was effective on the date on which it issued the approval letter, not the date on which the drug company received the letter. The FDA's interpretation is reasonable and enables it to fulfill its statutory mandate. Under 21 U.S.C. § 355(c), the FDA is required within 180 days of receiving an application for approval to either approve it or provide the applicant with notice of an op-

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[4] The FDA has since promulgated a regulation explicitly allowing approval based on draft labeling. *See* 21 C.F.R. § 314.105(b)(1986), which states:

> FDA will approve an application and issue the applicant an approval letter (rather than an approvable letter under § 314.110) on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

portunity for hearing on the question of whether the application is "approvable." Unless the FDA knows the date of notification, it cannot determine whether it fulfilled its statutory mandate.

"An agency's construction of a statute it is charged with enforcing is entitled to deference if it is reasonable and not in conflict with the expressed intent of Congress." *United States v. Riverside Bayview Homes, Inc.*, ___ U.S. ___, ___, 106 S. Ct. 455, 461 (1985) (citations omitted); *see also Aluminum Co. of America v. Central Lincoln Util. Dist.*, 467 U.S. 380, 389 (1984). "[I]t is not necessary that the agency's construction of the statute be the only permissible one. Rather, its construction 'must be upheld unless that view is plainly unreasonable.' " *Ohio v. Ruckelshaus*, 776 F.2d 1333, 1339 (6th Cir. 1985) (quoting *National Steel Corp. v. Gorsuch*, 700 F.2d 314, 321 (6th Cir. 1983)), cert. denied, ___ U.S. ___, 106 S. Ct. 2889 (1986).

We find that the FDA's determination that it had issued a valid approval for Buprenex in 1981 was a reasonable interpretation under the FFDCA and the regulations promulgated thereunder and was not in conflict with expressed congressional intent. Thus, we see no grounds for holding that the FDA's determination was not in accordance with law.

IV.

The Government further contends that the FDA's determination that Buprenex's approval date was December 29, 1981 did not violate the prohibitions in 5 U.S.C. § 706(2)(A) against arbitrariness or capriciousness. We agree.

In its citizen petition, Norwich asserted that the regulatory history of Buprenex was "unique and potentially confusing in that, although an 'approval' letter was sent to Norwich Eaton on December 29, 1981, there did not exist at that time FDA approved labeling under which the product could have been marketed." Joint Appendix at 26.

The company asked the FDA to declare that Buprenex was entitled to non-patent marketing exclusivity, asserting that the effective approval date was June 28, 1985, or, in the alternative, January 8, 1982. The FDA addressed each of the arguments raised by Norwich in its petition and concluded that the approval was effective on December 29, 1981.

The FDA began by rejecting Norwich's definition of "date of approval," as contained the Act, as meaning either the date on which a "meeting of the minds" occurred between the agency and the applicant as to the terms of the approval, or the date on which the applicant received the approval letter. The FDA also rejected Norwich's suggestion that an NDA could not be approved until the drug involved was cleared for marketing under the CSA. Rather, the FDA interpreted "date of approval" to mean "the date of [sic] which the agency exercises it authority under the Federal Food, Drug, and Cosmetic Act to approve a new drug application." Joint Appendix at 98.

The FDA pointed out that the language of its letter of December 29, 1981 clearly indicated that Buprenex was approved for marketing subject to Norwich making the agreed-upon changes in the label, and that FDA approval of the revised labeling was not a prerequisite to marketing. Under the provisions of the Act, the date of approval, not the date of marketing or distribution, determines whether exclusivity is available.

Kolbas' letter of February 3, 1982 to the FDA acknowledged that Buprenex was approved. Although the FDA admitted that it recommended additional changes to the labeling submitted by Norwich on January 27, 1982, it found these recommendations to be "irrelevant" to the date of approval. Norwich could have prepared final printed labeling in accordance with the December 29, 1981 letter and could have marketed Buprenex without further agency action. The 1981 letter requested submission only of final

printed labeling and a market package of the drug when available. Moreover, Dr. Finkel, of the FDA, had told Norwich on December 22, 1981, that draft labeling need not be submitted. Instead of preparing final labeling and marketing the drug, however, Norwich choose to submit a supplement containing draft labeling. The FDA assigned these submissions an "S" file number, indicating that it regarded them as supplements, not amendments, to the original NDA. ("Amendments" are used to modify pending applications. *See* 21 C.F.R. § 314.6 (1981 through 1984 eds.). "Supplements" effect changes in applications that have already been approved. See 21 C.F.R. § 314.8 (1981 through 1984 eds.).) Although the FDA commented on and suggested changes to this draft labeling, these submissions in no way prevented Norwich from going ahead and marketing Buprenex in accordance with the provisions of the 1981 letter.

The FDA asserted that its June 28, 1985 letter merely approved an amendment to the 1982 labeling supplement to the previously approved NDA. It pointed out that the 1985 letter was signed by a division director, who was authorized solely to approve supplemental, not new, drug applications. Thus, if the FDA were to accept Norwich's assertion that the 1981 approval was not effective, the 1985 "approval" still would not be effective since it would not have been approved by someone with proper authority.

The FDA then stated that Norwich was incorrect in thinking that ability to market a drug under the CSA was a condition precedent to approval under the FFDCA. The agency admitted that its letter of October 14, 1981 to Norwich erroneously indicated that final rulemaking under the CSA would be necessary before legal marketing could occur. As the December 29, 1981 letter stated, however, buprenorphine hydrochloride was scheduled at the time of the 1981 approval. Thus, Norwich could have marketed the drug at the time of the 1981 approval as a Schedule

II drug. Its decision not to do so was a marketing decision, not a result compelled by law.

The FDA acknowledged that a FDA employee had refused to certify Buprenex as being approved for marketing in the United States in December, 1984, pending the agency's receipt of the address of the manufacturing facility and copies of the final printed labeling. However, the agency asserted that this refusal reflected agency policy not to provide certification without this information. it did not indicate that the FDA did not consider the drug approved.

The FDA also noted that a copy of a May 12, 1982 recommendation of the Department of Health and Human Services to the DEA that buprenorphine hydrochloride be rescheduled was provided to Norwich's counsel. This recommendation clearly stated that the drug was approved, thus providing Norwich's counsel with notice of the agency's interpretation of the 1981 letter.

Finally, the agency admitted that Buprenex was initially included in the fifth edition of the agency's Approved Prescription Drug Products publication, but was omitted in later supplements. The FDA explained that Buprenex was dropped from the list because agency policy at the time was to list only those approved drugs being marketed. The agency stated that since it now appeared that Buprenex would be marketed, the drug would again appear in the publication.

In reviewing for a violation of 5 U.S.C. § 706(2)(A), "the court must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 416 (1971) (citations omitted). The reviewing "court may not concern itself with the wisdom of agency action." *Federal Property Mgt. Corp. v. Harris*, 603 F.2d 1226, 1230 (6th Cir. 1979) (citing *United states v. Allegheny-Ludlum Steel Corp.*, 406

U.S. 742, 749 (1972)). "The court is not empowered to substitute its judgment for that of the agency." *Overton Park*, 401 U.S. at 416. Rather, "[i]f the reasoning behind the agency's action is logical, . . . that action must be allowed to stand. That is true even if an alternative course of action would also be logical . . . . " *Harris*, 603 F.2d at 1231.

The FDA's denial of Norwich's citizen petition fully considered the arguments raised in the petition and rested upon a rational basis supported by the administrative record. Therefore, we find that the agency's determination in 1985 that Buprenex was approved in 1981 does not violate 5 U.S.C. § 706(2)(A).

V.

Accordingly, we REVERSE the District Court. The case is REMANDED to the District Court with directions to enter judgment for the Government.

APPENDIX B

NORWICH EATON PHARMACEUTICALS, INC.,
Plaintiff,

v.

OTIS R. BOWEN, SECRETARY OF HEALTH AND HUMAN SERVICES, ET AL.,
Defendants.

Civil No. C-1-85-1914

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF OHIO, WESTERN DIVISION

645 F. Supp. 321

March 3, 1986, Filed

Carl B. Rubin, Chief Judge

ORDER

This matter is before the Court following the presentation of evidence at a trial to the Court, and the filing of post-trial memoranda. Plaintiff Norwich Eaton Pharmaceuticals, Inc. (hereinafter "Norwich Eaton") seeks a declaration of its rights under Sections 505(j)(4)(D) and 505(c)(3)(D) of the Federal Food Drug and Cosmetic Act, 21 U.S.C. § 301 et seq. (FFDCA). Plaintiff also seeks an injunction requiring defendants Otis R. Bowen, et al. (hereinafter "defendants" or "the FDA") to recognize the appropriate non-patent exclusivity period for the marketing of BUPRENEX and preventing defendants from taking any action inconsistent with plaintiff's rights during that exclusivity period.

In accordance with Rule 52 of the Federal Rules of Civil Procedure, the Court does submit herewith its Findings of Fact, Opinion and Conclusions of Law.

I. FINDINGS OF FACT

1. Plaintiff, Norwich Eaton is an Ohio corporation engaged in the business of researching, developing, manufacturing and marketing pharmaceutical products.

2. Reckitt and Colman, Ltd. is a pharmaceutical company in England which holds the patent to the drug buprenorphine hydrochloride. Norwich Eaton is licensed by Reckitt and Colman to distribute buprenorphine hydrochloride in the United States under the trade name Buprenex Injectible (Buprenex).

3. Buprenex in an analgesic drug derived from the substance thebaine. By virtue of its derivation from the opiate thebaine, Buprenex is a narcotic drug subject to control by the Drug Enforcement Administration (DEA) under the Controlled Substances Act (CSA), 21 U.S.C. § 812.

4. On October 31, 1979, plaintiff filed a New Drug Application (NDA) with the Food and Drug Administration (FDA) for Buprenex. Prior to this time, buprenorphine hydrochloride had not been approved for marketing in the United States.

5. On October 14, 1981, Dr. Marion Finkel, M.D., of the FDA sent plaintiff a letter stating that the NDA for Buprenex would be approved if certain changes were made in the labeling. Dr. Finkel also cautioned that the drug was not marketable until final rulemaking procedures by the DEA. (Ex. A at 29-32)

6. On December 29, 1981 Dr. Finkel sent another letter to plaintiff in which she stated that, "the application is approved." (Ex. A at 36)

7. On January 27, 1982, plaintiff submitted to the FDA revised draft labeling incorporating the changes requested

by the FDA in its October 14, 1981 letter. (Ex. A at 38-54) This draft labeling did not include the controlled substance schedule of the drug. On May 24, 1982, the FDA replied to plaintiff, requesting additional changes to the labeling. (Ex. A at 56-58)

8. Further amendments to the labeling were filed by plaintiff in September, 1984 and February and March, 1985. (See Ex. A at 66) On February 28, 1985 the DEA ruled that buprenorphine hydrochloride is a Schedule V Narcotic Controlled Substance. (See Ex. A at 107) On June 20, 1985 the FDA made its final request for changes in the Buprenex labeling. (Ex. A at 66-70)

9. On June 24, 1985, the FDA received final printed labeling from plaintiff for Buprenex. On June 28, 1985 this labeling was approved. (Ex. A at 72) Plaintiff began marketing Buprenex on June 29, 1985.

10. Plaintiff filed a citizen petition on August 19, 1985 with the FDA regarding the exclusivity status of Buprenex. On December 6, 1985, the FDA, through the Secretary of Health and Human Services, ruled that the NDA for Buprenex was approved on December 29, 1981 and that therefore the exclusivity provisions of §§ 505(j)(4)(D) and 505(c)(3)(D) of the FFDCA did not apply to Buprenex.

II. OPINION

The Drug Price Competition and Patent Term Restoration Act became law on September 24, 1984. This amendment to the FFDCA was enacted to serve two purposes. Title I of the Act facilitates FDA approval of generic copies of pioneer drugs by permitting manufacturers to submit Abbreviated New Drug Applications (ANDA). Title II encourages research on new pioneer drugs by providing for an extension of patent rights to make up for time lost in performing the extensive testing required for FDA approval of a pioneer drug. In addition, Title I provides a limited period of protection from competition

through its exclusivity provisions under which the FDA may not make immediate approval of generic drug ANDAs or paper NDAs for certain previously approved pioneer drugs. §§ 505(j)(4)(D) and 505(c)(3)(D), FFDCA 21 U.S.C. § 301 et seq. The period of exclusivity, either 5 or 10 years, depends on when the pioneer drug's NDA was approved. NDAs approved prior to January 1, 1982 are not entitled to any period of exclusivity.

The present case turns on when the NDA for Buprenex was approved. Plaintiff asserts that the Buprenex NDA was approved either on June 28, 1985, when the final printed labeling was approved; or it was approved sometime in 1982 after plaintiff had submitted its revised draft labeling. Defendants, on the other hand, assert that the Buprenex NDA was approved on December 29, 1981 via Dr. Finkel's letter to plaintiff which specifically stated that "the application is approved." Moreover, defendants argue that plaintiff's claim is one for review under the Administrative Procedure Act and that the Court should find that the decision of the FDA was not "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law." (citing 5 U.S.C. § 706(2)(a)).

Upon review of the administrative record, the memoranda and the arguments by counsel, the Court finds that the Secretary's decision that the December 29, 1981 letter constituted final approval of the Buprenex NDA, is not substantiated in the record and is not in accordance with the FDA's own regulations.

Under the FFDCA plaintiff could not market the drug Buprenex in the United States until its NDA was effective. 21 U.S.C. § 335(a) Under 21 U.S.C. § 355(b), the sponsor of a new drug must submit "specimens of the labeling proposed to be used for such drug" in its NDA before the application will be considered. Moreover, the FDA has promulgated extensive regulations defining what must be in-

cluded in prescription drug labeling. 31 C.F.R. § 201.57(h)(1) provides:

> Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

The DEA did not issue its final rule on the scheduling of buprenorphine hydrochloride until February 28, 1985. Therefore, until that date, plaintiff's labeling submissions were, by the FDA's own definitions, insufficient for approval.

In other regulations, the FDA has stated its policy not to approve an NDA until labeling is in its final form. For example, 21 C.F.R. § 314.1(c) provides:

> 4(e) Typewritten or other draft labeling may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

However, according to 21 C.F.R. § 314.100(d), an NDA may achieve "approvable" status before final printed labeling is submitted.

> On the basis of preliminary consideration of an application or supplemental application containing type-written or other draft labeling in lieu of final printed labeling, an applicant may be informed that such application is approvable when satisfactory final printed labeling identical in content to such draft copy is submitted.

Clearly, and the parties agree, the October 14, 1981 letter from Dr. Finkel was notice of the "approvable" status of Buprenex in accordance with the FDA's ordinary practice under 21 C.F.R. § 314.100(d). It is equally clear that Dr. Finkel's letter of December 29, 1981 could be no more than a conditional approval of Buprenex. Although

plaintiff had agreed to the labeling changes requested in the October 14, 1981 letter, labeling was still not in its final form. No controlled substance schedule was included in the draft labeling as required by 21 C.F.R. § 201.57(h)(1). Indeed, labeling with the CSA schedule was not provided until March 11, 1985. Moreover, final printed labeling, which included the CSA schedule was not approved until June 28, 1985. Thus, the FDA's "approval" of the Buprenex NDA was contingent upon and not effective until approval of labeling in its final form.

For these reasons the Court holds that the effective date of the Buprenex NDA is June 28, 1985. Therefore, plaintiff under §§ 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the FFDCA, 21 U.S.C. § 301 et seq., is entitled to a five year exclusivity period for the drug Buprenex beginning June 28, 1985.

III. CONCLUSIONS OF LAW

A. This Court has jurisdiction pursuant to 28 U.S.C. § 1331 and 5 U.S.C. § 706.

B. Buprenex is a narcotic drug subject to control under the Controlled Substances Act and could not be marketed until the DEA ruled on its scheduling. 21 U.S.C. § 801 *et seq.*

C. A prescription drug subject to control under the Controlled Substances Act must include its CSA schedule on its label. 21 C.F.R. 201.57(h)(1); 21 U.S.C. § 825.

D. Defendant's decision that December 29, 1981 was the effective date for approval of the Buprenex NDA is not substantiated in the administrative record and is not in accordance with FDA regulations.

E. Approval of the Buprenex NDA was contingent upon approval of labeling in its final form and therefore not effective until June 28, 1985.

F. Plaintiff is entitled to five years exclusivity for the drug Buprenex beginning June 28, 1985 and ending June

27, 1990. §§ 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii), FFDCA, 21 U.S.C. § 301 *et seq.*

G. Defendants are hereby enjoined from approving any ANDAs or paper NDAs for generic equivalents of Buprenex until June 27, 1990. *Id.*

IT IS SO ORDERED.

APPENDIX C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Dec. 4, 1985

Kleinfeld, Kaplan and Becker
1140 Nineteenth Street, N.W.
Washington, D.C. 20036

Re: Docket No. 85P-0408/CP

Gentlemen:

This is in response to your citizen petition dated August 19, 1985 on behalf of Norwich Eaton Pharmaceuticals, Inc. regarding the status of its drug product Buprenex (buprenorphine hydrochloride) injectable under sections 505(j)(4) and 505(c)(3) of the Federal Food, Drug, and Cosmetic Act (the act). We are denying your petition for the reasons discussed below.

Action Requested

Petitioner requests that FDA declare that Buprenex Injectable is covered by sections 505(j)(4)(D)(i) or (ii) and 505(c)(3)(D)(i) or (ii) of the act. Petitioner requests the agency to include Buprenex in the next issue of the Approved Prescription Drug Products listings as having been approved on June 28, 1985 thus being entitled to exclusivity until June 28, 1990. Alternatively, petitioner requests the drug be listed as approved on January 8, 1982 thereby qualifying for exclusivity until January 8, 1992.

Statement of Grounds

Petitioner claims that Buprenex Injectable, containing a new chemical entity, has a regulatory history that is so unique and potentially confusing that, although an approval letter was sent to Norwich Eaton on December 29, 1981, there did not exist at that time FDA approved labeling under which the product could have been marketed. When labeling believed to be called for by FDA's December 20, 1981 letter was submitted to the agency, it was not ac-

cepted, and further changes were required before the labeling was acceptable to FDA. Petitioner claims final labeling was approved for the first time on June 28, 1985 and this date should be considered the approval date, not December 29, 1981.

Alternatively, petitioner argues that if the December 29, 1981 letter could be construed as full approval of the product and its labeling, the date of receipt of that letter (January 8, 1982) is the earliest date on which approval could be regarded as effective. Petitioner claims that FDA's letter of October 14, 1981, stated the agency's usual policy on the approval of drug products for which scheduling action is pending under the Controlled Substances Act. Based on this letter, Norwich Eaton alleges that it was its understanding that prior to receipt of the December 29, 1981 letter approval of Buprenex was conditioned upon completion of scheduling proceedings before the Drug Enforcement Administration. Therefore, until Norwich Eaton received a copy of the December 29, 1981 approval letter on January 8, 1982, petitioner states that it had no reason to believe that the agency would allow the marketing of the drug at that time.

In addition, petitioner points out that the tenth supplement to the Approved Prescription Drug Products publication, covering approvals through June 30, 1985, continued to indicate incorrectly that buprenorphine is not an approved drug. Petitioner contends that if FDA fails to list Buprenex Injectable as a post 1981 approved drug, manufacturers of generic products would receive the impression, which petitioner characterizes as erroneous, that the product is a pre-1982 approved drug not entitled to exclusivity under sections 505(j)(4)(D) or 505(c)(3)(D).

Petitioner also states that the agency may have already determined that the December 29, 1981 letter did not actually constitute approval because the agency's Approved Prescription Drug Products list shows buprenorphine in-

jectable as an approved product through the 5th edition (1984) but supplements to the 5th Edition show the drug as having been deleted, indicating the drug had not been finally approved. Petitioner, therefore, claims approval was on June 28, 1985 when labeling submitted in a supplement was approved.

Agency Response

Your petition raises the question what the term "date of approval" in the cited statutory provisions means. The agency interprets that term to mean the date of which the agency exercises its authority under the Federal Food, Drug, and Cosmetic Act to approve a new drug application. We reject your suggestion that approval does not occur until there has been a "meeting of the minds" between the agency and the applicant as to what the terms of the approval are. We also reject the suggestion that an approval is not effective until the applicant receives the approval letter. Similarly, we do not agree with the idea, which is implicit in some of your arguments, that a new drug application cannot be approved by this agency until the drug covered by the application has been cleared for marketing pursuant to the Controlled Substances Act.

The agency agrees with petitioner that Buprenex (buprenorphine hydrochloride) Injectable was a new chemical entity when approved. That drug was approved on December 29, 1981 in the letter of that date attached to your petition. This letter clearly states: "We [FDA] have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the labeling. As discussed in a telephone conversation between Dr. Alexander Neill and Dr. Marion J. Finkel on December 22, 1981, you have agreed to the conditional Phase IV bioavailability study and the labeling revisions outlined in our October 14, 1981 letter. Accordingly, the application is approved." The letter neither states nor implies that marketing had to wait until FDA approved the revised

labeling. Such approval was not needed for marketing because the labeling had already been agreed upon by phone by both parties. Thus, no additional agency action was necessary in order for Buprenex to be marketed. The provisions of §§ 505(j)(4)(D)(i) and (ii) and 505(c)(3)(D)(i) and (ii) of the act are, of course, not dependent upon the dates of marketing or distribution of the drug product as a basis for granting exclusivity, but, among other factors unrelated to time, only upon the date of approval. If marketing was a pivotal consideration for exclusivity, then § 505(j)(4)(D) and (c)(3)(D) would have been written in the manner of § 505(j)(4)(B)(ii)(I) under which exclusivity may be dependent on the date of marketing.

There was, at the time, no doubt on petitioner's part that the December 29, 1981 letter represented approval of its new drug application. Thus, in a February 3, 1982 letter, John M. Kolbas, President of petitioner, asked the then Bureau of Drugs Director, J. Richard Crout, for a meeting in a letter that began with the following sentence: "The Office of New Drug Evaluation approved Norwich Eaton's New Drug Application for buprenorphine hydrochloride injectable (Buprenex) on December 29, 1981."

The fact that the agency recommended additional changes to the labeling submitted on January 27, 1982, is irrelevant to the date of approval of the NDA for Buprenex. Based on the phone conversation of December 22, 1981 and the agency's letter of December 29, 1981, the petitioner could have prepared final printed labeling incorporating the changes set forth in the agency's letter of October 14, 1981 and marketed the product without additional agency action. The December 29, 1981 letter asked only for submission of final printed labeling and a market package of the drug when available, and, as petitioner's own memorandum of telephone conversation attests, on December 22, 1981, FDA's Dr. Finkel told petitioner's representative that draft labeling need not be submitted. Nevertheless, instead of preparing such final printed labeling, the

petitioner chose to submit a supplement containing draft labeling. (There is no question that FDA regarded this submission as a supplement to an approved application rather than an amendment to an unapproved application. The letter commenting on this labeling is identified by the number NDA 18-401/S-001. NDA 18-401 is the number of the approved new drug application and S-001 signifies the first supplement). It was the draft labeling submitted in this supplement that was commented on and to which additional changes were recommended. While these same changes would probably have been requested if final printed labeling had been submitted in accordance with the request made in the December 29, approval letter, those changes could have been made within some agreed upon timeframe, and that would not have prevented the marketing of Buprenex because it was an approved drug.

The letter of June 28, 1985, which petitioner now claims is the actual "approval" date for Buprenex, instead clearly approves an amendment to the 1982 labeling supplement to the previously approved new drug application. Furthermore, the letter of June 28, 1985, which petitioner claims to be the approval letter, was signed by Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products. There was no delegation of authority then, nor is there now, for a division director to approve a new drug application for a new chemical entity (see 21 CFR Part 5). Such delegation was and is limited to the Director and Deputy Director, Center for Drugs and Biologics and the Director and Deputy Director, Office of Drug Research and Review (see 21 CFR 5.80). A division director was, however, authorized to approve supplemental new drug applications (see 21 CFR 5.80). If the agency were to accept petitioner's position that the December 29, 1981 letter did not grant approval to the NDA, the result would be that the NDA was never approved because Dr. Leber lacks authority to approve it. Unapproved new drug products do not qualify for marketing protection under the act.

In addition, the marketing of such an unapproved new drug product is a violation of section 301(d) of the act which prohibits the introduction or delivery for introduction into interstate commerce of any new drug unless an approval of a new drug application is effective with respect to the drug. The agency also disagrees with petitioner's alternative argument that January 8, 1982 should be the approval date. As mentioned above, the exclusivity provisions are dependent only on the approval date of a drug product, not the date the approval letter was received by the applicant.

You suggest that, until it actually received the December 29, 1981 approval letter on January 8, 1982, petitioner expected that the approval letter "would have stated that the approval of the drug is contingent upon the completion of scheduling proceedings by the Drug Enforcement Administration and the submission of final printed labeling incorporating the appropriate labeling or the schedule in which the drug was placed." (See the August 6, 1985 letter, incorporated by reference in your petition.) As previously noted, an application is approved when FDA approves it, not when the applicant understands that approval has occurred. In any case, for several reasons, petitioner's purported misunderstanding of what the approval letter would say is difficult for petitioner to justify.

The October 14, 1981 letter on which the purported misunderstanding was based was in fact very clear, stating: "Upon successful completion or agreement of the aforementioned, you will be notified in writing that your application is approved" (see the second exhibit to your petition). The fact that the letter then stated that the product, even after that approval, could not be legally marketed until scheduling by the Drug Enforcement Administration was completed illustrates that the agency did not consider ability to market under the Controlled Substances Act to be a condition precedent to approval under the Federal Food, Drug, and Cosmetic Act. In any

case, as petitioner presumably was aware, the latter sentence represented an apparent misunderstanding at the time that letter was written that final rulemaking under the Controlled Substances Act would be necessary before legal marketing under that statute. As petitioner was aware, it was the agency's position that petitioner's product was already scheduled as a controlled substance because that product is a thebaine derivative, though FDA was moving to have the schedule changed. (Petitioner later contested the propriety of the classification of buprenorphine as a narcotic, but, in his February 3, 1982 letter, petitioner's president stated that "buprenorphine is presently controlled as a Schedule II substance as a result of its derivation by synthesis from thebaine.") Thus this was not even an example of a situation, which sometimes occurs, in which a new drug application is approved by FDA but the drug may not yet be marketed because of a need to comply with the separate requirements of the Controlled Substances Act.

The scheduling action that was pending was to consider rescheduling buprenorphine from Schedule II to Schedule V. It was not to place an unscheduled drug, into the appropriate schedule under the Controlled Substances Act. Because buprenorphine was classified in Schedule II at the time the NDA was approved, it was obvious that the drug could have been marketed upon FDA approval. The December 29, 1981 approval letter states this fact explicitly, stating that the agency's effort to reschedule buprenorphine "in no way impairs your approval to market buprenorphine in its current controlled substances schedule." The decision to withhold marketing until the drug was changed from Schedule II to Schedule V was apparently a marketing decision, but it was not based on any prohibitions under the act or the Controlled Substances Act.

Petitioner points, as one basis for its conclusion that its application was not approved in 1981, to a telephone statement by an FDA employee that a requested letter certi-

fying the approval of the application (sought by petitioner to obtain permission to market its drug in Jordan) could not be issued until the agency received copies of complete final printed labeling for the product (see the August 6, 1985 letter incorporated by reference in your petition). Petitioner characterizes this statement as "the agency's refusal to certify in 1984 that the product was approved for marketing in the United States" (see the August 6, 1985 letter). In fact, whenever anyone requests such a certificate, the agency requests, as it did in this instance, the address of the manufacturing facility and copies of the complete final printed labeling. As that request is made in all instances (most of which can be presumed to involve approved applications), the request is in no sense a basis for concluding that FDA did not regard the buprenorphine application as approved.

There is, moreover, very clear evidence, known to petitioner's counsel, that FDA regarded petitioner's new drug application as having been approved in 1981. Thus, the Department of Health and Human Services' May 12, 1982, recommendation to the Drug Enforcement Administration that buprenorphine be rescheduled states unequivocally that: "In December 1981, buprenorphine HCl (Buprenex) was approved as a parenteral analgesic for the relief of moderate-to-severe pain." (Copy provided to petitioner's counsel by letter of June 4, 1982).

The agency also disagrees with the petitioner's assertion that the omission of Buprenex from the current supplement of the agency's Approved Prescription Drug Products publication indicates Buprenex is not an approved new drug. Buprenex was approved on December 29, 1981 and was initially included in the 5th Edition of the list of approved prescription drugs. It was not included in later supplements, however, because it was agency policy at that time only to include in the list approved prescription drug products that were being marketed. Thus, when it was determined that Buprenex was not being marketed, it was

removed from the list. Now that it appears that Buprenex will be marketed, it will again appear in the Approved Prescription Drug Products publication. It will be added to Table IV, not because of exclusivity, but because patent information is filed.

Sincerely yours,

/s/ PAUL PARKMAN
for HARRY M. MEYER, JR., M.D.
Director
Center for Drugs and Biologics

APPENDIX D

21 C.F.R. § 201.57(h) (1986):

(h) "Drug Abuse and Dependence": Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse: This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) Dependence: This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse affects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

21 C.F.R. § 314.1(c)(2)(item 4.e.) (1981):

(c) Applications for drugs for human use shall be assembled and submitted in the manner prescribed by paragraph (e) of this section. . . .

Attached hereto, submitted in the form described in § 314.1(e) of the new-drug regulations, and constituting a part of this application are the following:. . .

4. *Copies of the label and all other labeling to be used for the drug* (a total of 12 copies if in final printed form, 4 copies if in draft form): . . .

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug. . . .

21 C.F.R. § 314.10 (1981): New drug application approvals; availability of information.

When a new drug application or a supplement to an approved new drug application is approved for a drug intended for humans, the approved labeling will be placed on file with the Food and Drug Administration, Office of Public Affairs, 5600 Fishers Lane, Rockville, MD 20857, for review by any person properly and directly concerned. The Press Relations Staff will make available weekly lists of such approved applications and supplements.

21 C.F.R. § 314.50 (1986):

(c) Summary. (1) An application is required to contain a summary of the application in enough detail that the reader may gain a good general understanding of the data and information in the application, including an understanding of the quantitative aspects of the data. . . .

(2) The summary is required to contain the following information:

(i) The proposed text of the labeling for the drug, with annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling, and, if the application is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57. . . .

21 C.F.R. § 314.100 (1981):

(d) On the basis of preliminary consideration of an application or supplemental application containing typewritten or other draft labeling in lieu of final printed labeling, an applicant may be informed that such application is approvable when satisfactory final printed labeling identical in content to such draft copy is submitted.

21 C.F.R. § 314.105 (1986):

(a) The Food and Drug Administration will approve an application and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the application apply. The date of the agency's approval letter is the date of approval of the application. When FDA sends an applicant an approval letter for an antibiotic, it will promulgate a regulation under § 314.300 providing for certification of the drug, if necessary. A new drug product or antibiotic may not be marketed until an approval letter is issued. Marketing of an antibiotic need not await the promulgation of a regulation under § 314.300.

(b) FDA will approve an application and issue the applicant an approval letter (rather than an approvable letter under § 314.110) on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

(c) FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for those drugs demand flexibility in applying the

standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet them. FDA makes its views on drug products and classes of drugs available through guidelines, recommendations, and other statements of policy.

21 C.F.R. § 314.125 (1986):

(b) FDA may refuse to approve an application for any of the following reasons: . . .

(2) The investigations required under section 505(b) or 507 of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling.

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

(6) The proposed labeling is false or misleading in any particular.

(7) The application contains an untrue statement of a material fact.

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in Part 201. . . .

APPENDIX E

21 U.S.C.A. § 355 (West Supp. 1986):

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall

publish information submitted under the two preceding sentences.

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3)(A) An applicant who makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give the notice required by subparagraph (B) to—

(i) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and

(ii) the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

(B) The notice referred to subparagraph (A) shall state that an application has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.

(C) If an application is amended to include a certification described in paragraph (2)(A)(iv), the notice required by subparagraph (B) shall be given when the amended application is submitted.

(c) Period for approval of application; period for notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) Approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) Give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportu-

nity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under the subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required

by paragraph (2) of such subsection shall be made effective on the last applicable date determined under the following:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (3)(B) is received. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (3)(B) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(i) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval may be made effective on the date of the court decision,

(ii) if before the expiration of such period the court decides that such patent has been infringed, the approval may be made effective on such date as the court orders under section 271(e)(4)(A) of Title 35, or

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture

or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of such court decision.

In such an action, each of the parties shall reasonably cooperate in expediting the action. Until the expiration of forty-five days from the date the notice made under paragraph (3)(B) is received, no action may be brought under section 2201 of Title 28 for a declaratory judgment with respect to the patent. Any action brought under such section 2201 shall be brought in the judicial district where the defendant has its principal place of business or regular and established place of business.

(D)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a new drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has

been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant,

the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the in-

vestigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions: or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the pro-

posed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. . . .

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (6) (hereinafter in this subsection referred to as a "listed drug");

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for

the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B)(i) An applicant who makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give the notice required by clause (ii) to—

(I) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and

(II) the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

(ii) The notice referred to in clause (i) shall state that an application, which contains data from bioavailability or bioequivalence studies, has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of such drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.

(iii) If an application is amended to include a certification described in subparagraph (A)(vii)(IV), the notice required by clause (ii) shall be given when the amended application is submitted.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds—

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dos-

age form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(3) Subject to paragraph (4), the Secretary shall approve an application for a drug unless the Secretary finds—

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C)(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show—

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title,

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (5), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(4)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined under the following:

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(I) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of the court decision,

(II) if before the expiration of such period the court decides that such patent has been infringed, the ap-

proval shall be made effective on such date as the court orders under section 271(e)(4)(A) of Title 35 or

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commerical manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of such court decision.

In such an action, each of the parties shall reasonably cooperate in expediting the action. Until the expiration of forty-five days from the date the notice made under paragraph (2)(B)(i) is received, no action may be brought under section 2201 of Title 28 for a declaratory judgment with respect to the patent. Any action brought under section 2201 shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(iv) If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection continuing such a certification, the application shall be made effective not earlier than one hundred and eighty days after—

(I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or

(II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier.

(C) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(D)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity

or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

(5) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended—

(A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(6)(A)(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public—

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this section before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (5) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list—

(i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (5), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that

the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(7) For purposes of this subsection:

(A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if—

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. . . .

Supreme Court, U.S.
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No. 86-1633

In the Supreme Court of the United States

OCTOBER TERM, 1986

NORWICH EATON PHARMACEUTICALS, INC.,
PETITIONER

v.

OTIS R. BOWEN, SECRETARY OF HEALTH
AND HUMAN SERVICES, ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

BRIEF FOR THE RESPONDENTS IN OPPOSITION

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QUESTION PRESENTED

Whether the Food and Drug Administration acted arbitrarily or capriciously when it decided that the date on which the agency had approved petitioner's new drug application for the drug Buprenex was December 29, 1981, and, on the basis of that factual finding, concluded that petitioner was not entitled to benefit from exclusive marketing provisions that are reserved by statute for drugs approved after 1981.

TABLE OF CONTENTS

	Page
Opinions below	1
Jurisdiction	1
Statement	2
Argument	9
Conclusion	13

TABLE OF AUTHORITIES

Cases:

Chevron U.S.A. Inc. v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984)	12
Inwood Laboratories, Inc. v. *Ives Laboratories, Inc.*, 456 U.S. 844 (1982)	3
Mobil Oil Corp. v. *FPC*, 417 U.S. 283 (1974)	9
United States v. *Generix Drug Corp.*, 460 U.S. 453 (1983)	2, 3
United States v. *Rutherford*, 442 U.S. 544 (1979)	12
Universal Camera Corp. v. *NLRB*, 340 U.S. 474 (1951)	9
Vermont Yankee Nuclear Power Corp. v. *Natural Resources Defense Council, Inc.*, 435 U.S. 519 (1978)	13
Weinberger v. *Hynson, Westcott & Dunning*, 412 U.S. 609 (1973)	2
Young v. *Community Nutrition Institute*, No. 85-664 (June 17, 1986)	12

Statutes and regulations:

Controlled Substances Act, 21 U.S.C. (& Supp. III) 801 *et seq.*	4, 11
Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585	3

Statutes and regulations—Continued: Page

Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. (& Supp. III) 301 *et seq.*:

21 U.S.C. (Supp. III) 355(a) (§ 505(a)) 2
21 U.S.C. (Supp. III) 355(b) (§ 505(b)) 2
21 U.S.C. (1976 ed.) 355(b)(6) 8, 11
21 U.S.C. (Supp. III) 355(b)(1)(F) 8
21 U.S.C. (Supp. III) 355(c) (§ 505(c)) 2
21 U.S.C. (Supp. III) 355(c)(1) 10
21 U.S.C. (Supp. III) 355(c)(3)(D)(i) 3
21 U.S.C. (Supp. III) 355(c)(3)(D)(ii) 3
21 U.S.C. (Supp. III) 355(d) 10
21 U.S.C. (Supp. III) 355(d)(1) 11
21 U.S.C. (Supp. III) 355(d)(6) 11
21 U.S.C. (Supp. III) 355(j)(4)(D)(i) 3
21 U.S.C. Supp. III) 355(j)(4)(D)(ii) 3, 8

21 U.S.C. (1976 ed.) 812(c) 7

21 C.F.R.:

Section 5.1(a)(1) (1981) 2
Section 5.10(a)(1) 2
Section 5.80(a) (1981) 2
Section 5.80 2
Section 10.30 5
Section 130.10 (1963) 3
Section 310.300(b)(4)(i) (1981) 5, 10
Section 314.1(c)(4)(e) (1981) 11
Section 314.105 (1981) 2-3, 6, 9
Section 314.105(a) 3

Miscellaneous:

28 Fed. Reg. 6377 (1963) 3
46 Fed. Reg. 26052 (1981) 2
50 Fed. Reg. 8104 (1985) 5
H.R. Rep. 98-857, 98th Cong., 2d Sess. (1984) 3

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BRIEF FOR THE RESPONDENTS IN OPPOSITION

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-14a) is reported at 808 F.2d 486. The decision of the district court (Pet. App. 15a-21a) is reported at 645 F. Supp. 321. The decision of the Food and Drug Administration (Pet. App. 22a-30a) is unreported.

JURISDICTION

The judgment of the court of appeals was entered on January 9, 1987. The petition for a writ of certiorari was filed on April 9, 1987. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

1. a. The Federal Food, Drug, and Cosmetic Act of 1938 established a system of premarketing clearance for drugs. *United States* v. *Generix Drug Corp.*, 460 U.S. 453, 458 (1983); *Weinberger* v. *Hynson, Westcott & Dunning*, 412 U.S. 609, 612 (1973). Section 505(a) of the Act, 21 U.S.C. (Supp. III) 355(a) prohibits any person from introducing into interstate commerce any "new drug" for which the Food and Drug Administration (FDA) has not approved a "new drug application" (NDA). Section 505(b) of the Act, 21 U.S.C. (Supp. III) 355(b), requires that an NDA contain: (1) reports of tests that show the drug is safe and effective for its intended use; (2) the drug's components and composition; (3) a description of the methods and controls used in manufacturing, processing and packing; (4) samples of the drug if the Secretary so requires; and (5) specimens of proposed labeling for the drug. Section 505(c) of the Act, 21 U.S.C. (Supp. III) 355(c), requires that the Secretary must approve or disapprove an NDA within 180 days of its submission, subject to extension by agreement of the parties. See *Weinberger* v. *Hynson, Westcott & Dunning*, 412 U.S. at 613.[1]

Under a regulation promulgated under the Act when the agency approves an NDA it is required to provide written notice to the applicant "that the application is approved and the application shall be approved on the date of the notification." 21

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[1] The authority to approve new drugs, granted by statute to the Secretary of Health and Human Services, has been delegated to the Commissioner of Food and Drugs (21 C.F.R. 5.1(a)(1) (1981); see 46 Fed. Reg. 26052 (1981); 21 C.F.R. 5.10(a)(1)), and to certain other specified officials of the FDA (21 C.F.R. 5.80(a) (1981); 21 C.F.R. 5.80 (1987)).

C.F.R. 314.105 (1981). That regulation, as subsequently amended, today provides that "[t]he date of the agency's approval letter is the date of approval of the application." See 21 C.F.R. 314.105(a) (1987). The prior version of this regulation had been in force since 1963. 21 C.F.R. 130.10 (1963); 28 Fed. Reg. 6377 (1963).

b. The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, amended the Act to provide a streamlined procedure for the approval of so-called generic drugs, which are copies of original, or "pioneer," drugs already approved by the FDA. See H.R. Rep. 98-857, 98th Cong., 2d Sess. 14 (1984); see also *United States* v. *Generix Drug Corp.*, 460 U.S. at 454-455; *Inwood Laboratories, Inc.* v. *Ives Laboratories, Inc.*, 456 U.S. 844, 846-848 & nn. 4, 5 (1982). The streamlined approval format, known as an Abbreviated New Drug Application (ANDA), is designed to enhance the competition between generic drugs and pioneer products by reducing the costs and time of obtaining regulatory approval to market generic drugs.

As part of the legislative compromise underlying the 1984 amendments, Congress provided that pioneer drugs approved by the FDA after January 1, 1982, would be entitled to certain periods of marketing exclusivity independent of that provided by patent: a pioneer drug containing a new chemical entity approved between January 1, 1982, and September 24, 1984, is entitled to ten years of marketing exclusivity (21 U.S.C. (Supp. III) 355(j)(4)(D)(i) and 355(c)(3)(D)(i)); a pioneer drug containing a new chemical entity and approved after September 24, 1984, the effective date of the 1984 amendments, is entitled to five years of exclusivity (21 U.S.C. (Supp. III) 355(j)(4)(D)(ii) and 355(c)(3)(D)(ii)).

2. a. Petitioner is a pharmaceutical company that filed an NDA on October 31, 1979, seeking approval of its pioneer analgesic drug, Buprenex, which contains the active ingredient buprenorphine hydrochloride. After an examination of the product's safety and effectiveness, and of the product's proposed labeling, the FDA, on October 14, 1981, notified petitioner that changes in the product's proposed labeling would be required before the product could be approved (Pet. App. 2a, 5a, 27a-28a). Subsequently, in a December 22, 1981, telephone conversation, petitioner agreed to the labeling changes (*id.* at 24a).

On December 29, 1981, FDA's Associate Director for New Drug Evaluation wrote to petitioner, stating that the Buprenex NDA had been approved. Because buprenorphine hydrochloride, the active ingredient in Buprenex, is derived from the opiate thebaine, it is a narcotic drug subject to the Controlled Substances Act, 21 U.S.C. (& Supp. III) 801 *et seq.*, which is administered by the Drug Enforcement Agency (DEA). When the FDA approved the new drug application for Buprenex in December 1981, buprenorphine hydrochloride was classified by the Controlled Substances Act as a Schedule II drug, but proceedings were in progress to place the drug onto a less restrictive schedule. In approving Buprenex, the FDA stated that the drug could presently be marketed as a Schedule II drug despite any on-going rescheduling proceedings before DEA. The December 29, 1981, approval letter stated (Pet. App. 3a):

> We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the labeling. * * * Accordingly, the application is approved.

> As you know, the Division is preparing documents to affect lesser controls for buprenorphine. This, however, in no way impairs your approval to market buprenorphine in its current controlled substances schedule.

In a letter to the FDA dated February 3, 1982, petitioner's president unequivocally acknowledged that the agency's "Office of New Drug Evaluation approved Norwich Eaton's New Drug Application for [Buprenex] on December 29, 1981" (Pet. App. 25a; see *id.* at 3a; C.A. App. 383). Petitioner thereafter provided FDA with the quarterly, semi-annual and annual reports required for approved new drugs. See Pet. 10; 21 C.F.R. 310.300(b)(4)(i) (1981).

On February 28, 1985, the DEA concluded its proceedings concerning the rescheduling of buprenorphine hydrochloride; it placed that substance on Schedule V of the Controlled Substances Act, the least restrictive category for substances subject to control under that statute. See 50 Fed. Reg. 8104 (1985).

b. On August 19, 1985, almost four years after the FDA had approved the NDA for Buprenex, and several months after the effective date of the 1984 amendments, petitioner filed a "citizen's petition" with the FDA under 21 C.F.R. 10.30, seeking a declaration that Buprenex qualified for non-patent marketing exclusivity under the 1984 amendments because the NDA for the drug Buprenex had been approved after January 1, 1982. Petitioner stated that although the agency issued a letter approving the Buprenex NDA on December 29, 1981, "there did not exist at that time FDA approved labeling under which the product could have been marketed" (C.A. App. 26). Petitioner claimed that as of December 29, 1981, Buprenex had not been assigned a schedule un-

der the Controlled Substances Act that was acceptable to petitioner. In addition, petitioner contended that final labeling was not approved until June 28, 1985, after buprenorphine hydrochloride had been rescheduled by DEA, and that this latter date was therefore the date on which the NDA filed in 1979 was actually approved. Under this theory, petitioner claimed that it was entitled to a five-year period of marketing exclusivity under the 1984 amendments. In the alternative, petitioner argued that the approval of its product occurred not on the date the FDA approval letter was issued (December 29, 1981), but on the date the letter was received (January 8, 1982). Under this alternative theory, petitioner claimed that it was entitled to a ten-year period of marketing exclusivity.

c. The FDA denied the petition (Pet. App. 22a-30a). In its opinion, the agency concluded that the letter of December 29, 1981, had unequivocally approved the NDA for Buprenex; that the statutory term "date of approval" refers to the date on which "the agency exercises its authority * * * to approve a new drug application" (see 21 C.F.R. 314.105 (1981)), not to the date an approval letter is received; and that approval is not contingent on a meeting of the minds between the FDA and the applicant on the terms of the approval. The agency explained that an NDA is approved when the statutory requirements for approval are met. Pet. App. 24a-29a.

In response to petitioner's assertion that Buprenex could not have been approved on December 29, 1981, because the drug was not then "scheduled" by DEA, the agency stated (Pet. App. 28a) that classification within a particular schedule under the Controlled Substances Act is not a statutory prerequisite to ap-

proval of a drug, and that, in any event, the drug's active ingredient, buprenorphine hydrochloride, was a derivative of the drug thebaine and therefore was statutorily classified as a Schedule II drug at the time the NDA for Buprenex was approved (see 21 U.S.C. (1976 ed.) 812(c)). Accordingly, the agency explained, Buprenex could have been marketed as a Schedule II drug on the date its NDA was approved.

The agency also rejected petitioner's contention that the Buprenex NDA was not approved until June 28, 1985, the date on which the FDA approved certain labeling for the drug. First, the agency noted, the June 28, 1985 letter stated that it constituted approval of an amended *supplemental* application—not approval of the original NDA which had been approved in 1981 (Pet. App. 26a). The FDA also observed that the letter of June 28, 1985, upon which petitioner relied, was signed by an agency official who, while having authority to approve supplemental applications, lacked authority to approve NDAs (*ibid.*). As the agency explained, even if petitioner were correct in contending that the Buprenex NDA had not been approved prior to June 28, 1985, the letter of that date could not constitute such approval and, in that event, petitioner had no authority to market its drug at all and no basis to claim exclusivity (*id.* at 26a-27a).

3. Petitioner challenged the agency's decision by commencing this lawsuit; it sought a declaration that the Buprenex NDA had been approved on June 28, 1985, and that petitioner was therefore entitled to a five-year period of marketing exclusivity under the 1984 amendments. The district court granted the relief petitioner requested. It held (Pet. App. 19a) that the agency's letter of December 29, 1981, was

only a "conditional approval." In the court's view, an approval could not be other than conditional until the product had final printed labeling containing a designation under the Controlled Substances Act that was satisfactory to the applicant (*ibid.*). The court concluded that final labeling was not approved until June 28, 1985, after Buprenex's classification under the Controlled Substances Act was changed from Schedule II to Schedule V. On that premise, the court held that Buprenex was not approved until June 28, 1985, and therefore that petitioner was entitled to a five-year period of marketing exclusivity under 21 U.S.C. (Supp. III) 355(j)(4)(D)(ii).

4. The court of appeals unanimously reversed. As a threshold matter, the court determined (Pet. App. 6a) that the only issue before it, and the only issue properly before the district court, was whether the FDA had acted arbitrarily or capriciously or had abused its discretion in deciding that Buprenex had been approved on December 29, 1981.

Turning to the merits, the court held that the FDA's interpretation of when a drug is approved, viz., on the date which appears on the approval letter, "is reasonable and enables [the agency] to fulfill its statutory mandate" (Pet. App. 9a). The court found nothing in the statute or regulations that would prevent the FDA from approving Buprenex on the basis of proposed labeling, since the Federal Food, Drug, and Cosmetic Act requires the applicant only to submit specimens of the labeling " 'proposed to be used for such drug' " (*id.* at 8a (quoting 21 U.S.C. (1976 ed.) 355(b)(6) and 21 U.S.C. (Supp. III) 355(b)(1)((F)). Thus, in the court's view, the statute "cannot be read to require submission of final printed labeling before approval" (Pet. App. 8a).

ARGUMENT

The decision of the court of appeals is correct and does not conflict with any decision of this Court or of any other court of appeals. The decision below is fact-specific and hence does not present a question of importance other than to the parties. Further review is therefore not warranted.

1. As the court of appeals recognized, the sole question at issue in this case is whether the FDA's denial of petitioner's citizen's petition was arbitrary or capricious. The agency's determination of the particular date on which petitioner's NDA for Buprenex was approved, a conclusion in which the court of appeals concurred, does not merit review on certiorari. Cf. *Mobil Oil Corp.* v. *FPC*, 417 U.S. 283, 310 (1974); *Universal Camera Corp.* v. *NLRB*, 340 U.S. 474, 491 (1951).

In any event, the FDA's determination that the date on which petitioner's new drug application had been approved mandated a denial of petitioner's request for exclusivity under the 1984 amendments was not arbitrary or capricious. In construing the term "approved" in the Federal Food, Drug, and Cosmetic Act, the FDA concluded that a new drug application is considered approved on the date stamped on the approval letter. See 21 C.F.R. 314.105 (1981). In this case, the FDA approved petitioner's new drug application in a letter dated December 29, 1981. Given that date of approval, the FDA was clearly correct in determining that petitioner's drug Buprenex did not qualify for the exclusive marketing benefits that the Act reserves for drugs approved on or after January 1, 1982.

The FDA's determination that the new drug application for Buprenex was approved on December

29, 1981, is thus supported by the agency's regulation governing when an NDA is approved and by the express language of the approval letter, which states unequivocally that "the application is approved" (Pet. App. 3a). Indeed, that determination is further corroborated by the acknowledgment by petitioner's president, on February 3, 1982, that Buprenex had been approved by the FDA on December 29, 1981, and by petitioner's subsequent filing of the quarterly, semi-annual and annual reports required by 21 C.F.R. 310.300(b)(4)(i) (1981) for *approved* drugs.

2. a. Petitioner contends (Pet. 18-22) that an NDA cannot be approved unless the agency has approved final printed labeling, as opposed to draft labeling, and that final labeling cannot be approved unless and until the drug has been assigned to a schedule under the Controlled Substances Act which is acceptable to the pharmaceutical manufacturer. Petitioner therefore claims that the FDA approval of Buprenex on December 29, 1981, was merely conditional, and hence was an insufficient basis on which to conclude that petitioner is not eligible to benefit from the exclusive marketing provisions of the 1984 amendments.

Petitioner has incorrectly perceived the applicable law. The approval of a new drug under the Federal Food, Drug, and Cosmetic Act is not dependent upon scheduling under the Controlled Substances Act or upon the approval of final printed labeling. The FDA must timely approve a new drug application if none of the grounds for disapproval set forth in 21 U.S.C. (Supp. III) 355(d) is present. See 21 U.S.C. (Supp. III) 355(c)(1). Thus, if a product is found to be safe and effective when taken as the

proposed labeling directs, the drug must be approved (see 21 U.S.C. (Supp. III) 355(d)(1) and (d)(6)).[2] Drug scheduling under the Controlled Substances Act is irrelevant to FDA's approval process and is performed under the wholly separate authority of the DEA. See 21 U.S.C. (& Supp. III) 801 *et seq.* Had Buprenex been unscheduled by the DEA, it would have been approved as an unscheduled drug by the FDA. Here, however, it was placed in Schedule II by an Act of Congress and upon approval of the new drug application by the FDA, Buprenex could have been marketed as a Schedule II drug.

There are significant flaws in petitioner's suggestion that final approval of the drug by the FDA had to await further rescheduling action by the DEA. At the time the FDA approval letter was issued, proceedings were already underway to consider placing buprenorphine hydrochloride, Buprenex's active ingredient, into a less restrictive schedule that was more acceptable to petitioner. The drug approval system created would be unworkable if the FDA could not approve a new drug application that met all statutory criteria, simply because there was a possibility that the DEA might change the schedule of

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[2] The district court, in ruling that an NDA cannot be approved until the final printed labeling is approved, ignored the lack of such a requirement in the statute. Instead, the court cited (Pet. App. 19a) 21 C.F.R. 314.1(c)(4)(e) (1981), a regulation which provides that an NDA "will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug."

As the court of appeals correctly held, the use of the word "ordinarily" in the regulation assumes "that on some occasions the FDA will approve an application based on draft labeling" (Pet. App. 8a), which is exactly what occurred in this case.

the drug in question. Similar practical difficulties would exist if, prior to approving a new drug application, the FDA were required to achieve a "meeting of the minds" with the applicant over suitable scheduling—a subject over which the DEA presides. The statute does not require that the fate of a new drug application be determined by the DEA or left entirely to the predilection of the applicant.

b. Petitioner also claims (Pet. 22-29) the court of appeals erred by deferring to the FDA's interpretation of the statute it administers and the regulations promulgated thereunder. It is petitioner's submission that the FDA has no expertise in questions of non-patent exclusivity, that the agency did not engage in adequate factfinding procedures, and that the agency decision may have been biased.[3]

The short answer to these contentions is that this case involves the FDA's construction of a term in its operating statute and, as this Court has repeatedly held, substantial deference to the agency interpretation is required. *Young* v. *Community Nutrition Institute*, No. 85-664 (June 17, 1986), slip op. 5-6; *Chevron U.S.A. Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984); *United States* v. *Rutherford*, 442 U.S. 544, 553 (1979). The deference to which the agency is entitled is not diminished by petitioner's contention that the agency "failed" to engraft additional procedures onto the approval scheme Congress established in the Federal Food, Drug, and Cosmetic Act. The agency carried

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[3] Petitioner's charge of potential bias has no support in the record and petitioner has been unable to point to any such bias in this case. Indeed, the petition acknowledges (Pet. 28) that "in the present case, FDA may have no particular bias against Norwich * * *."

out the tasks Congress directed by evaluating the Buprenex NDA under the statutory criteria, which include safety, effectiveness, and proposed labeling. The agency was not required to do more and its rational determination was correctly upheld by the court of appeals. Cf. *Vermont Yankee Nuclear Power Corp.* v. *Natural Resources Defense Council, Inc.*, 435 U.S. 519 (1978).

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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